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PREDICTORS OF NEWBORN MACROSOMIA

BY

ANILA VERMA ©

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Master of Science
in
Medical Sciences
(Perinatal epidemiology & biostatistics)

DEPARTMENT OF MEDICINE

Edmonton, Alberta
Fall 1994

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance a thesis entitled 'Predictors of Newborn Macrosomia' submitted by Anila Verma in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences (Perinatology & Biostatistics).

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Date....Oct 6, 1994..........

To
Mukesh,
Kshitij and Rajat

ACKNOWLEDGMENTS

I take this opportunity to thank my supervisor Dr Nanette Okun for her guidance and support throughout this project. Discussions with her were always stimulating and provided appropriate feedback. I am grateful to Dr Gordon Flowerdew for making valuable suggestions and assistance in the design and the analysis of the study. I am also grateful to Dr David Olson and Dr DW Morrish for their useful comments and suggestions.

Special thanks to the Perinatal Research Center, Univ. of Alberta for continued support throughout the project. Dr Nestor Demianzcuk gave important input at crucial moments during the study. He also provided unrestricted access to the perinatal clinic and its resources. Congenial atmosphere and helpful attitude in the perinatal clinic, case-room and various stations at the Royal Alexandra Hospital deserve special acknowledgment and thanks. The staff at the Grey Nuns hospital also maintained support throughout the study.

Dr B F Mitchell always made himself available for discussions and guidance. He maintained a close watch on all aspects of the study. He was a source of inspiration.

Finally, thanks to the internists and the heads of obstetric units of the collaborating hospitals. The diabetic clinic staff at both the participating hospitals was extremely co-operative. Subjects who volunteered to participate in the study deserve much praise as they are the most important pillars of clinical investigations.

ABSTRACT

INTRODUCTION:

Interventions designed to prevent fetal macrosomia among gestational diabetic women have met with varying success. The relative importance of gestational diabetes mellitus (GDM) and maternal obesity to the development of macrosomia, independent of the confounding effects of other associated maternal and neonatal characteristics, still needs to be ascertained.

OBJECTIVES:

(1) to determine the relative importance of glucose intolerance and maternal obesity among other known factors, as risk factors for fetal macrosomia.
(2) to determine predictors of disproportionate fat distribution in newborns.
(3) to examine the relationship between various levels of glucose intolerance and macrosomia.
(4) to compile tables of normative, anthropometric newborn measurements.

STUDY DESIGN AND METHODS:

The design was that of a case-control study, with 209 macrosomic newborns (birthweight $\geq$4000g) selected as cases and 791 non-macrosomic newborns (birthweight <4000g) selected as controls.
All 1000 mother/newborn pairs were recruited 24-48 hours after delivery at the Royal Alexandra and the Grey Nuns hospitals in Edmonton. Data on various maternal & newborn characteristics were collected.

Three measures of disproportionate fat distribution as suggested by Sasanow et al[1] and Ballard et al[2] were considered : (i) ponderal index; (ii) ratio of mid-arm circumference to head circumference; (iii) ratio of abdominal circumference to head circumference.
GDM subjects received standard therapy.

Univariate and multivariate analyses were performed to examine the determinants of fetal macrosomia, both in terms of absolute weight and in terms of large-for-gestational age (>90th percentile). Similar analyses were conducted to determine the predictors of disproportionate fat distribution.

RESULTS:

The most important predictors of fetal macrosomia were maternal and fetal constitutional factors such as maternal pre-pregnancy weight, height, ethnicity, maternal birthweight and gender of the newborn.

We did not find any significant risk factors for disproportionate fat distribution other than newborn's birthweight.

Glucose intolerance does not appear to have a statistically significant independent or synergistic effect with maternal obesity on the outcome of macrosomia.

CONCLUSIONS:

The pathogenesis of macrosomia remains elusive. The study results suggest that by focussing attention on gestational diabetic women we may be overlooking a more appropriate target group such as obese gravida, in our effort to prevent macrosomia.

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ABBREVIATIONS

AC:HC	Ratio of Abdominal circumference to head circumference
AGA	Appropriate for gestational age
BMI	Body mass index
BPD	Biparietal diameter
Birth wt	Birth weight
CI	Confidence interval
CRL	Crown-rump length
GCT	Glucose challenge test
GD	Gestational Diabetes (code)
GDM	Gestational diabetes mellitus
IDDM	Insulin-dependent diabetes mellitus
GDI	Intermediate gestational diabetes
LGA	Large for gestational age
MAC:HC	Ratio of mid-arm circumference to head circumference
Macro	Macrosomia
NIDDM	Non-insulin-dependent diabetes mellitus
OGTT	Oral glucose tolerance test
OR	Odds ratio
PI	Ponderal index
PMR	Perinatal mortality rate
Pre-preg wt	Pre-pregnancy weight
SGA	Small for gestational age
SAS	Statistical analysis system
SPSS	Statistical package for the social sciences
Std.dev.	Standard deviation

CHAPTER 1

RATIONALE, OBJECTIVES & HYPOTHESES

RATIONALE FOR THE STUDY

The small for gestational age or growth restricted newborn has often caught the attention of researchers. A number of studies on the associated morbidity have been conducted with a view to improve the prognosis of such a newborn. A macrosomic newborn may also be at an increased risk due to associated morbidities of birth trauma, or childhood and adolescent obesity[1]. It is important to explore the predictive factors for newborn macrosomia so that appropriate preventive interventions can be instituted.

Difficulty has been encountered in identifying historical, clinical, and laboratory factors predictive of macrosomia. Birth weight may be influenced by the maternal or fetal constitutional, metabolic or genetic factors. Risk factors thought to be associated with newborn macrosomia are previous history of macrosomia, maternal weight, height, age, race, ethnicity, weight gain during pregnancy, parity, gestational age, paternal constitutional factors, fetal gender, and maternal metabolic factors of which glucose is the most modifiable.

These predictive factors have not been examined in studies of 'interventions' or 'therapy' designed to prevent macrosomia. After finding better perinatal outcomes among insulin-treated diabetic pregnant women, clinicians and scientists have aimed at achieving normoglycemia even among gestational diabetic women hoping to prevent fetal macrosomia; though with varying degrees of success[2 3 4 5 6 7]. Since gestational diabetes is strongly correlated with maternal obesity, there has been considerable debate as to whether macrosomia in women with GDM is attributable to their obesity or to their glucose profile[1 5 8 9 10 11].

The main objective of the study was to delineate the relative importance of gestational diabetes mellitus and maternal obesity as risk factors for newborn macrosomia, so that the interventions designed to prevent macrosomia are more precise and appropriately focused. Once fetal macrosomia is suspected, the challenge of detecting the fetal disproportionate growth still remains. Our study also sought to investigate predictors of disproportionate fat distribution in newborns.

OBJECTIVES

The specific objectives of the study were both analytic and descriptive.

Analytic Objectives:

(1) to determine the relative importance of maternal obesity and gestational diabetes mellitus as predictors of newborn macrosomia and to explore a possible synergistic effect between maternal obesity and GDM for the development of newborn macrosomia

(2) to determine the relative importance of maternal and neonatal characteristics as predictors of disproportionate fat distribution in newborns

(3) to investigate whether the extent of glucose abnormality as reflected by the plasma glucose values (see page 55 for definition) correlates with fetal macrosomia

Descriptive Objectives:

(1) to construct nomograms of anthropometric measurements of newborns

RESEARCH HYPOTHESES

I Macrosomia is more strongly predicted by the maternal genetic or constitutional makeup i.e. maternal obesity than by gestational diabetes mellitus.

II In pregnant women with impaired glucose tolerance, the glucose abnormality as reflected by the mean plasma glucose values is not a significant predictor of newborn macrosomia.

RELEVANCE AND CLINICAL SIGNIFICANCE

One of the most significant developments in the last few years has been the recognition that gestational diabetes mellitus (GDM) may not be associated with increased perinatal mortality and that the increased perinatal morbidity attributed to it may be less significant than was previously hypothesized[12]. The increased perinatal morbidity may be due to the confounding effects of maternal characteristics that are not adequately controlled. According to 1990 figures from Statistics Canada, 15% of all births result in newborns weighing ≥4000g[149]. Report from the National Center for Health Statistics (1985) shows that 10.92% of all births in the United States result in newborns weighing ≥4000g, whereas the prevalence of GDM averages 3%[13]. GDM has been thought to be a significant contributor of to the development of macrosomia. This could be because the main risk factors for macrosomia are very similar to those for GDM, such as maternal obesity compounded by excessive weight gain during pregnancy, increased maternal age and prolonged gestational age[12]. Similar risk factors for these two conditions have led to a speculation that GDM may be associated with all the morbidity attributable to macrosomia.

In spite of the lack of a convincing relationship between gestational diabetes mellitus and macrosomia, and the lack of evidence for a beneficial effect of tight glycemic control among gestational diabetics in the prevention of macrosomia, current recommendations are that every pregnant woman be tested for gestational diabetes, and if diagnosed, treated by therapy aimed at tight glycemic control[14]. Not only may we be over-diagnosing, and over-treating an entity that may not be related to the outcome we are trying to avoid, we may be neglecting a more appropriate target group on which to focus preventive and/or therapeutic measures. While, the usual clinical criteria for making therapeutic decisions regarding management of GDM rely solely on blood glucose levels, the investigators are divided in their opinion regarding the relationship between plasma glucose concentration and fetal birthweight[11 15 16 17 18].

Because of its association with shoulder dystocia and birth trauma, it is important to determine the factors for higher newborn birth weights. Rather than focus on the diagnosis of gestational diabetes and its treatment with strict glycemic control, perhaps we should devote more attention to the obese mother, either in terms of pre-pregnancy counseling, or by treatment aimed at changing the level of some still unknown circulating growth stimulating factor.

Our efforts should be directed towards determining the precise etiology of fetal macrosomia and thereafter devising appropriate therapeutic strategies to prevent it, rather than trying to change the maternal metabolic milieu and thereby hoping to contain the newborn's birthweight.

The challenge is not only to predict fetal macrosomia prenatally, but also to evaluate any anthropometric disproportionality in such a newborn. Modanlou et al.[19] and others[20 21 22] have suggested that as the macrosomic fetus grows, the size of the trunk increases out of proportion to the size of the head. Shoulder dystocia and difficult delivery have been correlated not only with a higher birthweight but also with disproportionate growth in the newborn. Anthropometric disproportion is more evident in the infant of a diabetic mother even in one whose birthweight is below 4000g[19]. One of the objectives of our study was to determine the predictors of anthropometric disproportionality. Pre-gestational diabetic subjects were excluded from this study.

Clinical Relevance of Nomogram Tables

There is a scarcity of published information on newborn, normative anthropometric measurements. Developmental process in utero is guided by genetic and metabolic influences. Body proportions presumably reflect the biochemical milieu and the nutritional balance in utero.

The role of newborn body proportions has been stressed in relation to shoulder dystocia during vaginal delivery. Usher[23] expressed that the diagnosis of abnormalities in body proportions such as achondroplasia, hydrocephalous, and microcephaly could be made at birth with greater accuracy if precise data were available on the range of variation in body proportions of normal newborns.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1

FETAL MACROSOMIA

A. DEFINITION AND INCIDENCE

According to the definition of the American College of Obstetricians and Gynecologists (1991), all newborn infants weighing 4500g or more are macrosomic. However, the most common definition of macrosomia is that of a birthweight equal to or exceeding 4000g[24 25 26]. Although an absolute weight is easy to determine, it fails to consider the influence of gestational age on birth weight. Defining macrosomia as large for gestational age (most commonly greater than or equal to the 90th percentile of population birth weight for a given gestational age) provides a partial solution to this problem.

Excessive birthweight is associated with an increased risk of maternal and neonatal injury. It is likely that these risks exist on a continuum and increase with birthweight; but categorizing fetal weight as macrosomia versus non-macrosomia based on the demonstration of increased morbidity according to an arbitrary cut-off level of weight can be helpful in devising appropriate clinical strategies and therapeutic measures.

Normal birthweights for gestational age may vary with geographic, socio-economic as well as ethnicity factors[24 27]. Worldwide, mean birthweights range from 2400g among the Lumi of New Guinea to 3830g among the Cheyenne in the United States[28 29]. According to 1990 Canadian figures from Statistics Canada, 15% of all births result in newborns weighing $\geq$4000g[30]. According to the census from the National Center for Health Statistics (1985), 10.92% of all births in the United States result in newborns weighing $\geq$4000g. The incidence for newborns with birth weight >4500gs is 1.5%[8]. Male predominance among macrosomic babies has been observed routinely.

Interestingly, the incidence of fetal macrosomia has been showing a temporal increase over the past almost 50 years[19 31](fig 1.1). The cause for this increase has been attributed to better antenatal care, better nutritional status of women and an increase in the proportion of term deliveries. In Canada, the percentage of singleton premature (<37 weeks) births was 8.3% in 1972 and 5.3% in 1986[32]. The mean birthweight of singleton infants increased by 4.1% from 1972 to 1986[32]. Of the singleton births, 6.9% of the infants weighed 2500g

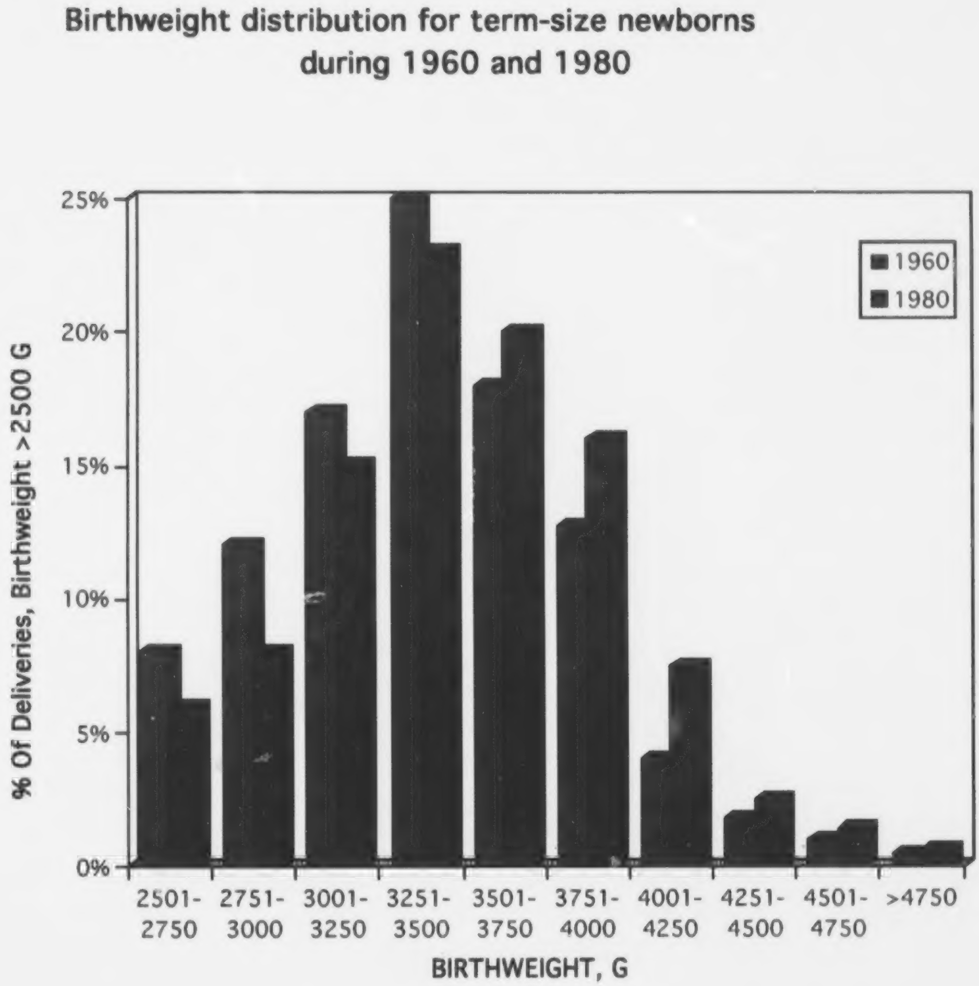


Fig 2.1 Values from a study by Modanlou et al[19], published in 1982, conducted at the Memorial Hospital Medical Center at Long Beach, USA.

or less in 1972; the figure decreased to 4.8% in 1986[32]. It is therefore recommended that the birth weight norms be updated every 5-10 years.

The etiology of fetal macrosomia is believed to be multifactorial. Potential predictors of macrosomia are grouped under two categories, namely genetic and metabolic[1]. The two categories can not be compartmentalized by rigid boundaries, as it is becoming increasingly clear that the metabolic milieu is largely influenced by the genetic makeup. As an example of the metabolic type, macrosomia in the infant of a diabetic mother is characterized by selected organomegaly, with increase in both fat and muscle mass resulting in a disproportionate increase in the size of the abdomen and shoulders. However, head circumference is not altered. Thus, it is suggested that the macrosomia of the insulin dependent diabetic (IDM) is asymmetric[33] and the macrosomic infant of a constitutionally big mother without carbohydrate intolerance will demonstrate symmetric macrosomia i.e. excessive growth of both the abdominal circumference and the head circumference. One of the objectives of our study is to explore possible predictors of disproportionate fat distribution in the newborns.

Among the other measures of fetal growth, Georgieff et al.[34] concluded that ratio of mid-arm circumference to head circumference (MAC:HC) is more useful than birthweight alone in assessing the quality of intrauterine nutrition and the likelihood of metabolic complications in neonates whose pattern of fetal growth has been accelerated or retarded. Among the macrosomic infants, the MAC:HC has been shown to distinguish large-for-gestational age (LGA) insulin dependent diabetes mellitus (IDM) infants from LGA-non-IDM infants[34].

Ratios like ponderal index (weight in kg x 100/length in m^3) and mid-arm circumference to head circumference (MAC:HC), are said to be relatively free of the influence of race, gender and gestational age at term[1 35].

B. DIAGNOSIS

So far, no single method or variable seems capable of predicting macrosomia in the antenatal period with acceptable accuracy. Unfortunately, the ability to predict macrosomia clinically remains poor, with only 35% of large infants being identified by excessive fundal height measurements[36]. Parks and Zie[37] found that, of 110 macrosomic babies, the diagnosis of macrosomia was made prenatally in only 20 percent of cases. Gross et al.[38] evaluated the predictive value of 17 different factors in various combinations, supposedly associated with shoulder dystocia in deliveries with macrosomic fetuses. The best classification obtained had a positive predictive value of only 15%. Thus the diagnosis of macrosomia is often not made until after the delivery.

Detection of the macrosomic fetus using ultrasonographic techniques also remains challenging. Although ultrasound can identify a group of fetuses with significantly increased risk of macrosomia, no current formula has a sufficiently accurate predictive value to be used independently in making clinical decisions[28]. The most widely used formula to estimate fetal weight ultrasonographically is that of Shepard and colleagues[39], in which estimated fetal weight is derived from the biparietal diameter and abdominal circumference. This formula predicts fetal weight with an accuracy of less than 25%. Tamura et al.[40] showed that macrosomia when greater than the 90th percentile can be predicted in 74% of cases using the Shepard formula. Typical accuracy in estimation of fetal weight near-term is ±15%[37]. With an inadequate knowledge about clinical predictors, it would need universal screening with ultrasound at term to identify a LGA, which will be too expensive even if somewhat accurate. Delpapa and Mueller-Heubach[41] analyzed outcomes of 242 women with sonographic estimates of fetal macrosomia and concluded that cesarean delivery or early induction to avoid continued fetal growth were inappropriate when based solely upon ultrasound diagnosis. Others have also urged caution in the use of sonographic estimations of fetal weight to guide obstetric decisions concerning labor and delivery[42].

C. PATTERN OF FETAL GROWTH

Population differences in growth are the result of both environmental and genetic factors, acting independently as well as synergistically. Enough data has been amassed from many world populations to show possible genetic patterns in growth, and almost 38% of the variation in birthweights can be attributed to heredity. The greater part of the variance, the remaining 62% is attributable to environmental and other causes[43 44]. The contribution of the fetus's own genes in determining its size at the time of birth is small, and the contribution of maternal factors, both genetic and environmental, is overwhelming. However, observations of human subjects and animal models of mice suggest that the uterine effect on fetal growth occurs late in gestation and probably does not affect the embryo during organogenesis. Recent experience with in vitro culture of embryos during the early stages of organogenesis suggests that the growth rate is an intrinsic property of the embryo not mediated by environmental influences[45].

Interactions between the uterus and the embryo for controlling fetal growth rate are a feature of late gestation only. The rate of growth is modified during the latter half of fetal life to produce a smooth progression in size. Although dietary recommendations for pregnant women abound, neither the maternal macro or micronutrient requirements for optimal fetal growth nor the interrelationships between them are adequately understood. The enzyme-mediated pathways modulating the use of nutrients for growth emerge at different rates and in different sequences in each fetal organ. The fetal growth is definitely influenced by nutrient availability for the mother and the fetus and the nutritional state of the mother before and during pregnancy.

From conception to delivery and beyond, the developing infant exhibits circumferential and linear growth resulting in continuous incremental increases in volume and mass. Fetal growth may be viewed as a net integration of stimulatory and inhibitory influences arising intrinsically and environmentally.

The embryonic period, which occupies the first 8 postovulatory weeks, is a time during which the structures of organs make their first appearance.

At the end of embryonic period the crown-heel length is approximately 39-47mm and the weight of the embryo is 2-2.7g[45].

Crown-rump length (CRL) can be measured from week 6 onward using ultrasound. Growth of the CRL from 6 to 14 weeks of pregnancy shows a rapid increase, doubling in size approximately every 10 days from 6-10 weeks, with a linear increase in velocity of 1.4 mm/week. During the 25th week, length velocity is 1.0 cm/week, increasing steadily to 1.3 cm/week between 31-32 weeks until 33-34 weeks. A gradual deceleration follows, so that in the 40th week, linear growth velocity is 0.5 cm/week[45].

Fetal weight is one of the most significant indicators of fetal growth and is linked with fetal well being. Fetal weight can be recorded directly and accurately on fetal material *ex utero* and on neonates. However, accurate assessment of gestational age is difficult to ascertain. Ultrasound has proved an immensely valuable tool for the study of fetal growth and physiology. Gender specific fetal weight estimates considered along with gestational age estimates ultrasonographically, provide the basis for recognition of normal/abnormal fetal growth patterns.

First Trimester:

(a) Gestation Sac: 5 weeks gestation; fetal pole and cardiac activity by 6 weeks gestation

(b) Crown-rump length(CRL): CRL<0.5cm size by 6weeks gestation; CRL is most reliable measure of gestational age between 7-14 weeks after the last normal menstrual period (LNMP)

Second and Third Trimester:

(a) Head Measurements: Satisfactory measurement before 20 weeks gestation permits an accuracy of ± 5 days in gestational age. Reliable predictions on gestaional age can be made up to 28 weeks of gestation as the normal range of head measurements is quite wide after that. The biparietal diameter (BPD) shows a steady linear increase from the time it can first be measured using ultrasound at 11-12 weeks to 28 weeks. The mean weekly increase drops from a value of 3-4 mm at 11-12 week to less than 1 mm at 40th week[46]. Biparietal diameter is least affected by intrauterine starvation and is therefore a good indicator of fetal maturity.

(b) Trunk Measurements and Head: Abdomen Ratios: Measurement of fetal abdominal circumference at a plane just superior to the umblicus may be used to assess both fetal age and fetal mass. Trunk measurements most accurately reflect changes in liver size. The abdominal growth velocity increases rapidly until 30 weeks gestation, after which the rate of increase diminishes in synchronism with BPD[46]. However, the rate of reduction in truncal growth after 30 weeks is much less than that of the head.

The ratio between the head size and the abdominal size is expected to become abnormal in babies with asymmetric growth pattern because of the brain-sparing effect during periods of under-nutrition or over-nutrition. Head:abdominal ratio is an important measure of this aberrant growth pattern. Ogata et al.[22] showed that in a group of 23 insulin-sensitive diabetics, the BPD measurements remained within normal limits, whereas abdominal growth was excessive.

(c) Fetal Weight: The most rapid period of fetal growth is during the 20 weeks between 12 and 36 weeks of gestation. Between 32 and 36 weeks, the rate of fetal weight gain reaches its peak at 200-225g/week[45]. After reaching the maximum weight gain, deceleration occurs. On average, deceleration begins when the fetus reaches 3000g in weight, but there are differences in the level of weight gained between populations. The formulae for estimation of fetal weight are associated with a 95% confidence range of at least 10-15%. Thus the predicted weight using ultrasonography would have to exceed 4,700g for all fetuses above 4000g, to be accurately identified.

Among fetuses with abnormal growth patterns, subcutaneous fat may be either reduced (IUGR) or increased (diabetic macrosomia). More commonly, accelerated fetal growth, particularly of the abdomen, is an indication of diabetic macrosomia.

D. REGULATION OF FETAL GROWTH

Fetal growth is controlled by multiple influences of fetal, maternal and placental origin, and their interactions. The complexity of the environment *in utero* makes it difficult to evaluate regulators of fetal growth singly. However, it is clear that some growth control in the embryo operates before any organ takes form and is a function of the embryo's own constitution. Hormones and growth factors appear to mediate the biological influences of many of these factors at the cellular level after the stage of embryogenesis.

(a) Insulin and Fetal Growth

Insulin is synthesized by the fetus from late in the first trimester onward, and insulin receptors are detectable from early in gestation. Insulin secretion, however, is not responsive to changes in blood glucose levels until the third trimester in humans. Although insulin has many anabolic actions besides stimulation of glucose uptake (stimulation of amino acid uptake and synthesis of protein, fat and glycogen), it does not stimulate mitosis of cultured cells at concentrations near physiological range. It remains to be ascertained whether the apparent cell-proliferative action of insulin found *in vitro* culture of rat cells is mediated in human fetus by somatomedins. Apparently, insulin is permissive for fetal growth and its growth-stimulatory actions are mediated by its effect on carbohydrate, protein, and fat metabolism rather than through direct stimulation of cellular proliferation[47]. Hyperinsulinimic infants of diabetic mothers may have increased birth weight but usually do not have increased birth lengths, so the increase in weight is primarily attributable to accumulation of fat in adipocytes.

(b) Insulin-Like Growth factors and Fetal Growth

Recent research has focused attention on the potential importance of insulin-like growth factors (IGF) in fetal growth. Insulin-like growth factors IGF-I and IGF-II are small molecular weight peptides with both mitogenic and metabolic properties. These peptides resemble proinsulin in structure and are thought to regulate cellular proliferation and other anabolic processes in many tissues[48]. These factors exert their physiological functions through an endocrine as well as an autocrine/paracrine mechanism of action. It is presumed that the IGF levels in plasma regulate the overall growth status, while locally produced IGFs are important for cell proliferation in specific tissues[49] [50]. IGFs circulate in association with specific binding proteins (IGFBPs) which are thought to modulate the availability and the biological effects of IGFs on target tissues[51]. IGF binding protein-3 is one of the six IGFBPs identified to date.

Nutritional factors are well-known to alter the concentrations of IGF-I and IGF binding proteins[52]. Such factors may be significant during pregnancy and be altered by diabetes. However, it is debatable whether systemic IGF-I contributes to the regulation of intra-uterine growth or it is a product of the developing feto-placental unit.

Previous studies have investigated IGF levels in maternal and cord blood, though often with conflicting results. Ashton et al.[53] in 1985 and more recently, Lassarre et al.[54] in 1991 found correlations between body weight, somatomedin activity and IGF levels in cord blood. Both found a significant correlation between IGF-I levels and fetal weight, but no such relationship for IGF-II.

(c) Placental Hormones and Fetal Growth

The placenta is an extraordinarily active endocrine gland that regulates fetal growth in many ways. In addition to its role in maternal-fetal steroidogenesis, the placenta synthesizes peptides that are homologous with hypothalamic releasing factors, pituitary hormones, and growth factors. Human placental lactogen (hPL) shares 91% homology with human growth hormone and is a weak promoter of growth in a variety of experimental systems.

(d) Fetal Growth & Interaction among Classic Hormones and Growth Factors

Many of the growth effects resulting from administration of growth hormone are apparently mediated by somatomedins. Tissue concentrations of epidermal growth factor and nerve growth factor are dependent on thyroid hormones and fibroblast growth factor is synthesized in response to glucocorticoids. The somatomedins might be dependent on placental lactogen and prolactin, as well as nutritional status and possibly thyroid hormone and insulin for their production and action. Growth factors may be considered mediatory hormones, mediating the action of classic hormones on target tissues[55].

(E) PREDICTIVE FACTORS FOR NEWBORN MACROSOMIA

(1) Maternal Pre-Pregnancy Weight

With an overall incidence of macrosomia of 1.7 per 1000, Spellacy et al.[8] found that only 5.1% of infants weighing more than 4500g were born to women with gestational diabetes. By comparison 44.6% were born to obese women and 10.8% to women beyond 42 weeks gestation.

Frequency of macrosomia with single associated high-risk factors

Table 2.1

Risk condition	No. of women with single risk condition	% Macrosomia* with each risk factor
Postmature > 42wk	1154	5.4
Obese > 90kg	3168	5.6
Gestational diabetes	453	6.4
Insulin-dependent diabetes	184	9.2
Obese > 112.5kg	487	10.0

*macrosomia defined as birthweight>4500g

Spellacy et al. also reported that for women weighing more than 90 kg, the percentage of obese women were 8.2% for 2500-3500g infants; 33% for 4500-5000g infants; and 50% for infants who weighed more than 5000g[8].

In another study among patients selected not on the basis of glucose intolerance, univariate analysis revealed a greater frequency of macrosomia among obese mothers than among non-obese mothers[56]. Even among gestational diabetics, a positive association has been demonstrated between birth weight and maternal pre-pregnancy body mass index (BMI)[10 57], percent ideal body weight[57] and absolute weight[26]. When grouped by pre-pregnancy BMIs, no significant differences were found in the incidence of LGA neonates between infants of gestational diabetics (treated) and those of non-diabetics[56].

(2) History of Macrosomia in the Past

There is an increased risk of delivering an infant weighing more than 4000g if a prior infant weighed more than 4000g[24 58].

(3) Weight Gain

Weight gain during pregnancy is directly proportional to birthweight, though the causal pathway is complex when relationship with pre-pregnancy weight is considered. Independent positive associations between fetal macrosomia and both pre-pregnancy weight and gestational weight gain have been demonstrated[59 60].

(4) Glucose Intolerance

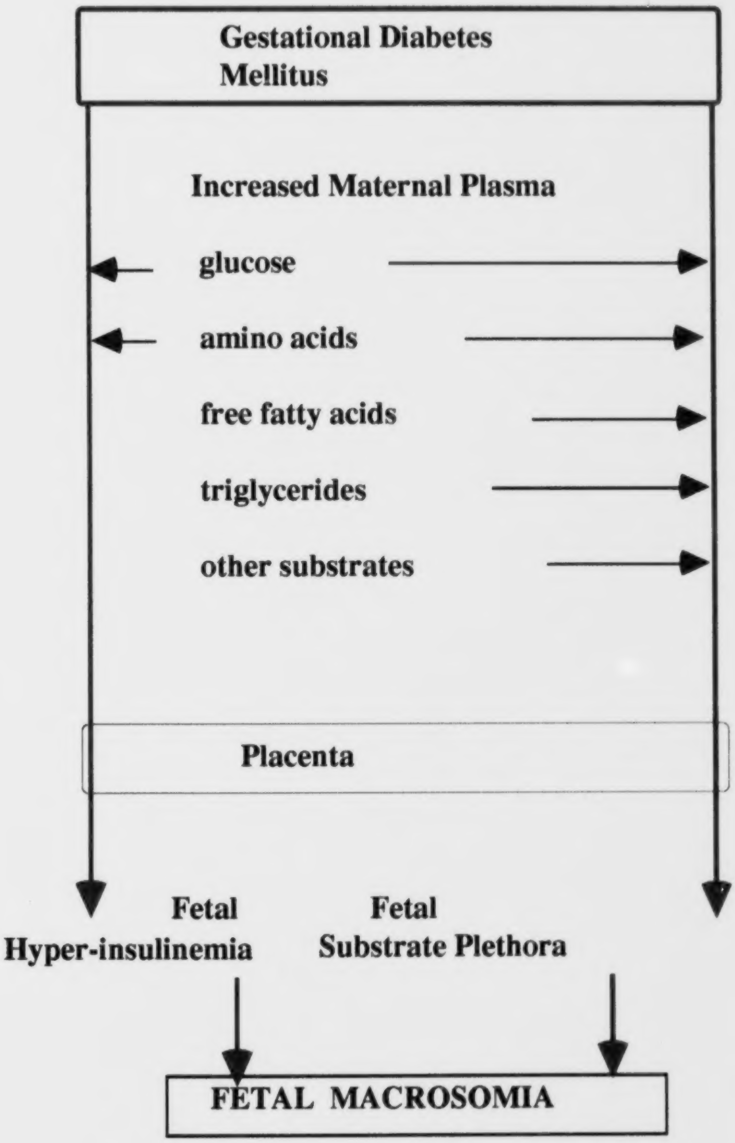
Macrosomia has long been the hallmark of diabetic fetopathy. Among infants weighing more than 4000g, the shoulder circumference and abdominal circumference of infants of the diabetic mothers are significantly greater than those in infants of the non-diabetic mothers[19 31]. Preferential growth in insulin-sensitive tissues (e.g. adipose, liver) probably accounts for some of these differences in growth patterns. It is a significantly important contributing factor to shoulder dystocia among the diabetic women.

Pathophysiology:

According to Pedersen[61] hypothesis which postulates that diabetes mellitus leads to fetal hyperglycemia through transplacental transport of excessive amounts of glucose from a hyperglycemic mother. Fetal hyperglycemia in turn leads to fetal hyperinsulinemia, increased anabolism and fat storage. This concept was later expanded by Freinkel[62] to include the concept of a generalized metabolic disturbance, in which other fuels (fats and amino acids) are also thought to be involved. Some investigators have found that cord blood insulin and C-peptide levels are increased and this has been interpreted as confirming enhanced fetal pancreatic islet cell activity, leading to fetal macrosomia[47 63 64 65].

Maternal plasma substrate profiling, although important to the understanding of metabolic control in GDM, does not quantitate the fluxes of glucose, amino acids and lipids from the maternal circulation into the placental-fetal unit and their ultimate metabolic disposition and impact on fetal size in diabetic pregnancies. The following chart (fig 2.2) illustrates the proposed scheme linking GDM and macrosomia.

Fig 2.2 Proposed scheme for the development of fetal macrosomia in gestational diabetes mellitus


Gestational Diabetes Mellitus
Increased Maternal Plasma
glucose
amino acids
free fatty acids
triglycerides
other substrates
Placenta
Fetal Hyper-insulinemia
Fetal Substrate Plethora
FETAL MACROSOMIA

Pathophysiologically, GDM may differ significantly from pre-gestational diabetes mellitus. In one study using regression analysis, only 4% of birthweight was attributable to maternal glucose intolerance[66] among gestational diabetics.

The relationship between maternal glucose levels and fetal macrosomia has been explored in several publications. Some have failed to demonstrate any significant relationship,[11 67 68 69] while others have found a positive correlation[5 70 71 72]. Lekin et al.[73] found that patients who had an elevated 1-hour glucose challenge test (GCT) value but normal oral glucose tolerance test (OGTT) results, delivered macrosomic babies significantly more than those having normal glucose screens. A progressive positive relationship between macrosomia and the 2-hour value on normal GTTs has also been reported[74]. These studies are in conflict with the one demonstrating a lack of relationship of neonatal macrosomia with either GCT values or single (2-hour) value on a GTT[75]. Neither is there enough evidence to prove that screening or treatment for GDM reduces perinatal morbidity associated with macrosomia[5 7 76 77]. It is difficult to make meaningful comparisons between these studies because of substantial differences in observational content or study design among studies dealing with this topic.

(5) Gestational Age

Spellacy[8] found an association of post-term pregnancy with macrosomia (see table 2.1 above). An increased risk of shoulder dystocia among post-dated macrosomics has been reported by Acker et al.[58] and Johnson et al.[56].

(6) Ethnicity

Dooley et al.[78] examined 92 subjects for influence of race on newborn's birthweight. They found that despite comparable degrees of carbohydrate intolerance across racial groups, mean birthweight was found to be highest in Hispanics and lowest in Blacks and Orientals[78].

(7) Multiparity

Parous women are overly represented among mothers of macrosomic babies[1], but it has not been determined whether parity is an independent predictor or is related through other factors, such as age.

(8) Male Sex

Male sex may be a risk factor. In most studies of fetal macrosomia, 60-70% of macrosomic babies are male[8 79]. In our study, sex-specific weight curves on gestational age have been used to make the diagnosis of large-for-gestational age, therefore avoiding bias due to overrepresentation of male babies.

(9) Maternal Height

The effect due to maternal height probably represents a small but important contribution due to constitution of the mother[44 59].

(10) Paternal morphometric measures

These morphometric measures haven't yet been fully explored, but have been shown to be likely predictive factors[44 81].

F. OTHER MEASURES OF FETAL GROWTH

Ponderal Index (P.I.= weight in kg x 100/length in m^3)

Ponderal Index assesses relative fatness or thinness by quantification of the dissociation of weight and length. Its use may be helpful as it is relatively independent of the influence of sex, race and gestational age at term[35]. The distribution of infants by birthweight differs significantly from the distribution by ponderal index. The P.I. is equal to, if not superior to 'birthweight for gestational age' as a tool to predict neonatal morbidity including asphyxia, acidosis, hypoglycemia and hypothermia in SGA babies[35].

Mid-Arm Circumference (MAC) &
Ratio of Mid-Arm Circumference to Head Circumference (MAC:HC)

Sasanow et al.[82] have shown that there is a predictable linear rise in both the MAC and MAC:HC with increasing gestational age and birthweight. MAC has been reported to be more accurate than birthweight, length and head circumference in discriminating between appropriate for gestational age (AGA) and small for gestational age (SGA) babies[83].

MAC:HC assesses body proportionality based on the principle of relative sparing of head growth compared with that of the muscle and fat during periods of under or over nutrition. The increase in MAC and in MAC:HC with gestational age reflects the deposition of fat stores in the upper arm as the percent body fat increases from less than 1% at 24 weeks to 14% at term[84]. MAC:HC has a theoretical advantage over ponderal index in reflecting body proportionality because it represents a ratio between the mid-arm circumference, an anthropometric measurement markedly affected by changes in nutritional status, and head circumference, the measurement least affected by nutritional status. The denominator in ponderal index, length^3 is not so much independent of the influence of nutritional status just as the numerator, the body weight.

G. MORBIDITY AND MORTALITY ASSOCIATED WITH MACROSOMIA

The risks of newborn macrosomia include increased incidence of cesarean section, birth trauma with attendant morbidity due to shoulder dystocia, trauma to maternal pelvic soft tissue following traumatic delivery and possibility of obesity in later life in the newborn[3 58].

Passage of the macrosomic baby through the birth canal may be associated with significant fetal morbidity and rarely even mortality. Studies from the 1970s and 1980s reveal neonatal mortality rates for macrosomic babies in the range of 2-3%, which is higher than that for controls of lower birthweights[85]. In general, more recent studies have not noted any increased mortality due to birth trauma in macrosomic babies[25 86]. Macrosomic babies are not more prone to birth asphyxia other than that due to the increased risk of birth trauma. The clinical relevance of macrosomia lies in its association with birth trauma; for example birthweight over 4000g has been associated with a risk of shoulder dystocia of 4.7% which increases to about 9.4% for infants weighing over 4500g, while birthweight under 4000g is associated with a shoulder dystocia rate of 0.3%[87].

Maternal morbidity related to the birth of a macrosomic fetus is predominantly that associated with cesarean delivery or trauma to pelvic soft tissue following a traumatic delivery. Spellacy et al.[8] in 1984 found cesarean section rate of 34% in women delivering infants weighing >4500g compared with 17% in mothers of babies weighing 2500-3499g. The increased incidence of cesarean delivery seems to be primarily related to dystocia. Given that the current methods for estimating birthweight prior to delivery are not dependable, it is not known whether the increased rate is related to the actual size of the infant or to the anticipation by the physician of a difficult delivery. Levine et al.[88] conducted a study in 1990-91 to determine whether the sonographic diagnosis of an LGA fetus at term affected obstetric management. They found that the sonographic prediction in that series was incorrect in half of the cases. The incorrect sonographic diagnosis of an LGA fetus had a statistically significant effect on both the diagnosis of labor abnormalities (18% vs. 29%, p=.04) and the incidence of elective cesareans (12% vs. 27%, p=.04) in pregnancies with appropriate for gestational age birthweights.

The reported rate of macrosomia in infants of women with GDM varies from 0.7%[52] to 25%[71], depending on the criteria for diagnosis of macrosomia. The mean birthweight for infants of gestational diabetics in the United States was 3466g, compared with a mean birthweight for normal infants of 3336g[89]. The clinical significance of this 130g difference in birthweight is debatable. In addition, the influence of other confounding factors on any difference in birth weight has not been assessed. A review[89] of many studies revealed a higher incidence of macrosomia in infants of women with GDM when compared with a control group (whatever way control group may be chosen). However, in most of the studies reviewed, the control group was not matched to the experimental group on various maternal characteristics that are known to produce confounding effects on the outcome of macrosomia. Further Stephenson[90] has also pointed out that in terms of morbidity, macrosomia could actually be only an intermediate outcome measure in a GDM woman; and birth trauma, the ultimate morbidity of concern is dependent not only upon the size of the baby but also on materno-pelvic factors and pattern of labor.

Glucose intolerance in pregnancy has also been linked to asymmetric fetal growth, which may cause over-development of the shoulders even if the birthweight is within normal limits. Modanlou et al.[19] showed that neonates of diabetic mothers experiencing shoulder dystocia had significantly greater shoulder-to-head disproportions compared to equally macrosomic infants of non-diabetic mothers delivered without dystocia. However, none of the studies relating glucose intolerance to birth trauma have differentiated pregestational from the gestational form of diabetes mellitus.

In three case-control studies that compared macrosomic infants with normal infants, macrosomic infants were 3-fold[91], 9-fold[92] and 19-fold[24] more likely to have shoulder dystocia. This wide variation in rates raises questions about the methodology of the studies and the definition of shoulder dystocia used. Levin et al.[92] retrospectively studied 13,870 singleton live births. The incidence rates of brachial plexus injury and clavicular fracture were 2.6 and 2.0 per 1000 respectively. In the group without trauma, 5.5% of the infants had macrosomia as compared with 38.9% of those with brachial plexus injury and 21.4% of those with clavicular fracture. Boyd, Usher and McLean[91] also found that brachial plexus paralysis and clavicular fractures are more frequent in infants weighing more than 4000g than in smaller infants (2.5% v 0.01% and 5.5% v 0.06% respectively). Again most of these studies have related birth trauma to macrosomia or to diabetes mellitus and have not distinguished pregestational IDM from GDM. The confounding factors known to influence birthweight such as fetal gender, parity, smoking status, age, ethnicity, type of labour, maternal weight and degree of glucose intolerance have not been taken into account. Johnson and colleagues reported that in pregnant women weighing more than 250 pounds, the incidence of shoulder dystocia was 5.1% compared with 0.6% for control women who weighed less than 200 pounds[56]. Coustan and Imarah[2] in study of the prophylactic insulin treatment in GDM subjects, found the incidence of birth trauma (shoulder dystocia, Erb's palsy, cephalhematoma, soft tissue injury) to be 4.8% in the insulin-treated group, 13.4% in the diet-treated group, and 20.4% in the untreated group ($p<.05$). In this study, there was no true random allocation of patients into the three categories of 'treatment with insulin and diet', 'diet al.one' and 'untreated', and also there was a lack of uniformity of gestational age at the time of recruitment i.e. patients anywhere between 20-36 weeks of gestational age were recruited. Data on plasma glucose levels during treatment in pregnancy was not available, making the results all the more suspect.

H. PREVENTING MACROSOMIA

Maternal caloric restriction has been proposed as a means of decreasing the supply of fetal substrate. Although there is a reported reduction in the incidence of macrosomia following reduction in caloric intake[93 139], the results are inconclusive because none of the trials have been properly controlled.

Obstetricians have sought early or planned inductions in infants suspected to be large for dates especially in women with impaired glucose tolerance. There are following objections to this strategy:

(1) Positive predictive value for identifying fetal macrosomia by both, the clinical and the ultrasonographic methods is inconsistent and is less than 50% at its best[36 37 38 39 40].

(2) Potential for harm exists in terminating pregnancy before full-term. This strategy has not been examined by randomized, controlled trials.

Another strategy to reduce fetal weight gain has been the use insulin to limit the availability of substrate to the fetus. There are three objections to the use of insulin for preventing macrosomia:

(1) There is a potential harmful effect of insulin on the infants of women with lower levels of glucose intolerance; e.g. Langer[16] reported a higher risk of developing small for gestational age babies with increasing use of insuiin.

(2) Despite insulin treatment, obese women have shown a higher incidence of macrosomia when the data were stratified by maternal glucose levels[94].

(3) There is also that risk of introducing undetected hypoglycemia in the mother in early pregnancy

CHAPTER 2

REVIEW OF THE LITERATURE
2.2
GESTATIONAL DIABETES MELLITUS

A. DEFINITION AND PREVALENCE

Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. This definition was proposed by the National Diabetes Data Group, endorsed at the Second International Workshop-Conference on GDM and reaffirmed in 1986 by the American Diabetes Association. The definition applies irrespective of the mode of treatment instituted. It does not exclude the possibility that the glucose intolerance may have antedated the pregnancy. By this definition, GDM occurs in about 1-3% of all pregnancies. As assessed by conventional diagnostic methods, it affects approximately 11,000 Canadian women per year. In three community based studies, the prevalences were 0.31%[95], 1.2%[96] and 3.1%[97]. Estimates of prevalence vary with the ethnic diversity of the population, the geographical area, the screening and the diagnostic test criteria. However, in general the glucose intolerance is mild and postpartum testing will reveal normal carbohydrate tolerance within 6 weeks in 95% of the cases. Importantly, about 40-50% of women with GDM ultimately develop overt diabetes in later life[85 98], and there is mounting evidence for long range complications that include obesity and diabetes in offspring born to these women[99].

An important correlate of glucose intolerance in pregnant women is obesity. Johnson[56] and colleagues reported that 8% of 588 women who weighed more than 250 lbs had GDM compared with 1% of women who weighed less than 200 lbs. Age also is an important contributing factor; Mestman[100] in 1980 reported that the incidence of gestational diabetes was 3.7% in women younger than 20 years, 7.5% for those between 20-30 years and 13.8% for women older than 30 years.

B. ETIOLOGY AND CLASSIFICATION

GDM represents a complex interrelationship and interaction of the genetics of susceptibility to various types of glucose intolerance and the normal metabolic and hormonal alterations of pregnancy. GDM is a heterogeneous disorder representing, at least in part, patients who are destined to develop either IDDM (insulin-dependent-diabetes mellitus) or

NIDDM (non-insulin-dependent-diabetes-mellitus) in later life[101] [102]. Pregnancy has been described as a 'controlled stress' state. The pregnancy related hormones (cortisol, progesterone, human chorionic somatomammotrophin, prolactin and estradiol), the so-called stress hormones result in excessive fuel delivery to maternal circulation that can not be metabolized and therefore results in hyperglycemia, hyperlipidemia, increased ketone formation, and lactic acid formation. Insulin which is also increased in pregnancy, attempts to produce and store protein, fat and glycogen. Any imbalance between these two processes would result in hyperglycemia.

It has been suggested that GDM could be due to decreased insulin receptor binding to target cells or increased resistance to insulin, with a relative lack of circulating insulin[103] [104]. Weiss and Coustan[105] have provided ample evidence that the diabetogenicity of pregnancy is related to a pronounced peripheral resistance to insulin. The resistance is probably brought about by cellular effects of the high plasma levels of one or more of the pregnancy associated hormones. There is also support in the literature for decreased binding affinity of the insulin receptor, a post receptor defect, or increased removal of insulin from the circulation, as contributors to insulin resistance[106] [107]. Most pregnant women are able to counteract the insulin resistance by a compensatory increase in both basal and nutrient-stimulated insulin secretion. However, a few seem unable to produce a sufficiently large increase in insulin secretion, and therefore glucose intolerance occurs.

Hence, this insulin resistance of pregnancy may unmask sub-clinical defects in carbohydrate homeostasis, not manifested in the non-gravid state. Normal pregnant women and normal weight gestational diabetic women have comparable fasting insulin levels, whereas the levels in obese GDM are considerably higher. The metabolic responses of the obese GDM women differ from those of the lean GDM women, emphasizing the heterogeneity of this disorder. The current classification of GDM includes two subgroups- Class A_1 and Class A_2. Differentiation between the two groups is based upon fasting blood glucose values.

Classification of GDM

Table 2.2

Class	Fasting Plasma		Post-prandial Plasma
A-1	<5.8mmol/l	and	<6.6mmol/l
A-2	>5.8mmol/l	and/or	>6.6mmol/l

C DIAGNOSIS OF GDM

The diagnostic criteria used to define carbohydrate intolerance in pregnancy vary between countries and institutions. The protocol being followed at most Canadian institutions has been adapted from the proceedings of the third international workshop-conference on GDM held in 1990. Guidelines for GDM screening and treatment have been provided by the Society of Obstetrics and Gynecology (SOGC) of Canada and the Canadian Task Force on Periodic Health Examination[108] in 1992. Both sources cast doubt on the validity of currently used diagnostic criteria and treatment approach.
Diagnosis involves a universal screening glucose challenge test followed by a definitive diagnostic test if the screen test is positive.

Protocol For Glucose Screen Test (GCT)

1. The test is given between 24-28 weeks of gestation to all women not diagnosed as glucose-intolerant up to that point. The test is done regardless of fasting or fed state.
2. A 50-g oral glucose load is administered orally.
3. Venous (not capillary) blood is drawn 1 hr later, and the plasma glucose level is measured. A value of 7.8mmol/l (140 mg/dl) or more is considered positive and indicates the need for a full oral glucose tolerance test.

About 15% of all pregnant women have an abnormal 1-hour screening test and 15% of these will be found to have GDM defined by at least two abnormal values using the results of oral glucose tolerance test. This method of screening has a sensitivity of 79%, and a specificity of 87%[109]. The sensitivity is 96.6%, when the borderline value is 7.22 mmol/l and 20.6% of all pregnant women would need an OGTT[110]. It has been considered that different thresholds are required for adequate sensitivity in different obstetric populations.

In North America, the definitive diagnostic test for GDM is a 100-g OGTT interpreted according to the National Diabetes Data Group (NDDG) criteria[111] set in 1979. In 1982, Carpenter and Coustan proposed stricter criteria for the diagnosis of GDM[112]; their values are also widely applied.

Protocol for Oral Glucose Tolerance Test (OGTT)

1. The oral glucose tolerance test is done after at least 3 days of unrestricted diet (>=150 g carbohydrate) and physical activity.
2. A 100-g oral glucose load is given in the morning after an overnight fast of at least 8 hrs but not longer than 14 hrs.
3. The venous plasma glucose level is measured at fasting and at hourly intervals for 3 hrs while the patient remains seated. Smoking is not allowed.
4. For diagnosis, two or more of the following plasma glucose concentrations must be reached or exceeded:

Criteria for Diagnostic Test-OGTT

Table 2.3

Time After OGTT	Glucose Level	
	NDDG Criteria	Carpenter and Coustan
At fasting	≥5.8 mmol/l (105 mg/dl)	≥5.3mmol/l (95 mg/dl)
After 1 hr	≥10.6 mmol/l (190 mg/dl)	≥10mmol/l (180 mg/dl)
After 2 hr	≥9.2 mmol/l (165 mg/dl)	≥8.6mmol/l (155 mg/dl)
After 3 hr	≥8.1 mmol/l (145mg/dl)	≥7.7mmol/l (140 mg/dl)

There is a lack of international agreement with regard not only to treatment but also diagnostic criteria of gestational diabetes mellitus. Consensus is not possible without agreement on the objectives in making the diagnosis. In the present context, the diagnosis is deemed to be important as a risk factor for adverse perinatal outcome in pregnancy; though the most commonly used criteria for an oral glucose tolerance test in North America were validated by their predictive value for the subsequent development of overt diabetes in later years and were based on a statistical approach to the definition of normality rather than on an adverse outcome.

The search for an ideal and cost-effective method of screening and subsequently diagnosing gestational diabetes continues in light of the fact that the present approach is neither as sensitive nor as specific as would be desirable, if the purpose is to reduce perinatal morbidity significantly. There remains a lack of consensus about the ideal threshold value for the GCT, testing in the fasting vs. fed state or using selective or universal screening[113] [114]. Part of the problem with GCT[114] and OGTT[113] is their lack of reproducibility. The most notable objection to this recommended screen is that the cut-off plasma glucose level was arrived at by comparison with an abnormal glucose tolerance test, and not by identifying women with increased perinatal morbidity.

In a thorough review, Naylor[113] pointed out major methodological flaws in generalization of O'Sullivan and Mahan's work. The OGTT, which is the gold standard for the diagnosis of glucose abnormality, has its own limitations. The criteria for the OGT test were derived in the 1950s from an unrepresentative sample of women tested predominantly in the later stages of pregnancy. Measurements were made with the now outdated Somogyi-Nelson whole blood glucose technique, and test translation errors are present in the threshold values proposed for modern plasma glucose oxidase methods. The threshold values were set on an arbitrary statistical basis by adding 2SD to the mean whole-blood glucose for each time stage of OGTT. The other limitation of this diagnostic test is that the reproducibility of OGTT results has not been determined. The reproducibility of OGTT is good in only about 70% of pregnant women with normal carbohydrate metabolism. In women with impaired glucose tolerance (IGT) or GDM, the reproducibility is even less[110].

Although GDM is now diagnosed with a view to adverse maternal-fetal outcome in the index pregnancy, the criteria for a positive test were validated with respect to the maternal risk of developing glucose intolerance over the ensuing 8 years as shown by a 75-g OGTT in the non pregnant state.

D. PERINATAL MORTALITY AND MORBIDITY ASSOCIATED WITH GDM

It was not until 1973 that O'Sullivan et al.[85] attempted to link an abnormal glucose tolerance test to perinatal mortality. When the authors analyzed perinatal mortality according to age, weight, and glucose tolerance, they noted that the increased perinatal mortality rate (PMR) in the presence of a positive glucose tolerance test was confined to women aged 25 years or more, and also was more common among obese women (refer to table 2.4). It is notable that there was no perinatal mortality in gestational diabetic women aged less than 25 years. Authors were of the opinion that both maternal age and weight play a comparatively minor role in negative control patients as compared with gestational diabetic patients but no plausible explanation for this dichotomy was provided.

PMR and Maternal Age & Weight in normal and gestational diabetic subjects

table 2.4

Age in years	Percent Relative Weight	Positive OGTT		Negative OGTT	
		numbers	Perinatal %	Deaths numbers	%
<25	<120	0/40	0	2/138	1.4
	>120	0/13	0	1/33	3
>25	<120	4/54	7.4	0/54	0
	>120	8/80	10	1/34	3.9
All Patients		12/87	6.4*	4/259	1.5*

Fisher's exact test: * p = 0.007

Major objection to that landmark study is that the two groups being compared have been selected from different time periods. Gestational diabetic population was selected from 1962 to 1970; whereas the control population was a systematiclly selected control group picked over a 15-month period starting in 1967. Interventions to the two groups of subjects were also not same. Control group was not matched to the gestational diabetic group on any confounding variables, such as gestational age, maternal age, obesity, and socioeconomic status. It may well be these variables that caused the perinatal mortality rate of 6.4% in women with gestational diabetes, and not the presence of GDM per se. In addition there was no mention of the cause of death or the age of the neonate at the time of death. The impact of different time periods for selection of controls vs. cases on perinatal mortality was also not examined.

Gabbe et al.[3] compared the perinatal death rate among the infants of 261 women with GDM (followed up between 1970 and 1972) with the rate in the general population of the same hospital. The rates were 32 and 19 per 1000 respectively. Sutherland and Stowers[115] in 1975 reported results of 1800 intravenous glucose tolerance tests done on 1600 women during pregnancy with various indicators suggestive of diabetes. The study highlighted that the rate of fetal loss increases eight fold ($p<.001$) as the number of indications for glucose tolerance testing increase from one to four, and that the risk of fetal death for each indication is not revised significantly by the presence or absence of glucose tolerance. It is quite possible that the increased risk of perinatal mortality is predicted as much by the indication for glucose tolerance testing, as by the test result itself. In the existing literature linking GDM with perinatal mortality and morbidity, the confounding effects due to maternal characteristics, such as obesity, ethnicity, pre-existing diabetes and hypertension, are hard to discern and quantify.

In past studies, PMR ascribed to glucose intolerance has ranged from 0%[70] to 28.5%[116], but three major factors affect these ranges:

First is the general decline in PMR to the current overall PMR in Canada of 5.7 per 1000 total births for birthweight of 1000 g or greater[30].

Second, studies have insufficient power to determine whether PMR is (statistically) significantly higher in women with GDM.

Third, a review of the literature demonstrates that studies on mortality have failed to control for other prognostic factors like neonatal weight and gestational age[116].

Therefore the actual PMR due to glucose intolerance has remained unascertainable. A prospective, randomized, controlled trial (RCT) with perinatal mortality rate as its primary outcome will be ideal to draw conclusions regarding the relationship between perinatal mortality rate and the diagnosis of GDM. But the sample size for such a design would be unfeasible.

Coustan and Imarah[2] analyzed retrospectively the outcome of 445 pregnancies involving women with gestational diabetes managed between 1975 and 1980. Three therapeutic interventions were compared: a classic prenatal diet not specific to diabetes, a strict diabetic diet and fixed insulin therapy in addition to the diabetic diet. Adverse outcomes were less frequent in the insulin group than in the untreated group and the diet-alone group. The insulin group showed reduction in the rate of macrosomia, operative delivery, and birth trauma. These study results need a closer scrutiny in view of the fact that the confounding variables were not taken into account, and also, a woman had to have at least two of the classic risk factors for GDM to be included in the study.

Thompson et al. randomized subjects to treatment with diet al.one versus diet and insulin[117]. The mean birth weight was significantly reduced in the insulin treated group by 414g ($p=.002$) and the incidence of macrosomia (>4000g) reduced by 20% (26.5% vs. 5.9%, $p<0.05$). This difference was most pronounced in mothers weighing >200lbs. There was no difference of maternal glycemic levels between groups. There was also no difference in operative delivery, shoulder dystocia; or neonatal hypoglycemia, hypocalcemia or hyperbilirubinemia.

Fetal morbidity measures of metabolic disturbances such as hypoglycemia, hypocalcemia and hyperbilirubinaemia may[118 119] or may not be[26 120] related to GDM; the available relevant literature is conflicting. Though the short-term and the long-term effects of hypoglycemia are unclear, still hypoglycemia is a frequently cited cause of neonatal morbidity in infants of women with GDM. In the literature the incidence ranges from 0%[121] to 20%[122]. A review of these studies reveals that:

1) study samples were small
2) confounding variables like gestational age and birthweight were not always taken into account e.g. a study by Lubchenco revealed an incidence of hypoglycemia of 66.7% in infants who were small for gestational age, compared with only 4.2% in infants who were large for gestational age[123].
3) most of these studies have not differentiated between gestational and pre-gestational diabetes mellitus.
4) maternal treatment with insulin may confound the results
5) there are few data on the prognosis of patients with mild or asymptomatic hypoglycemia[124].

Hypocalcemia is the next most commonly cited neonatal complication of GDM, with a reported occurrence of 0%-10%[121] [125]. Generally, as the quality of study design improves, the reported rate of hypocalcemia in the study falls. Hyperbilirubinaemia of >12 mg/dl occurs in 6%[126] to 50.6%[26] of neonates of GDM mothers, a range similar to that in the control group. In the past, iatrogenic prematurity among babies of GDM mothers may also have been responsible for hyperbilirubinaemia.

In addition to the above, other yet unresolved adverse perinatal outcome includes congenital anomalies. Infants born to insulin-dependent diabetic mothers have a 2 to 7.9 times higher risk of having major congenital malformations[127]. GDM, on the other hand does not seem to be associated with an increased incidence of birth defects[128]. A propensity to develop future obesity and diabetes mellitus has been noted in the progeny of women with GDM[99].

E. MATERNAL MORBIDITY

It is likely that GDM alone does not cause any maternal morbidity related to pregnancy. Some of the older literature suggests an association between GDM and pre-eclampsia[124], but others have refuted this in the more recent literature[129]. Also, the quoted increased risks of pregnancy induced hypertension, postpartum hemorrhage etc.. have not been determined in randomized, controlled trials. Investigators have shown that patients with gestational diabetes mellitus are at an increased risk of developing diabetes later in life[98 99]. O'Sullivan[85] has shown development of overt diabetes beyond 20 years following pregnancy among GDM women to be as high as 20% and that of impaired glucose tolerance to be 50%.

With the literature being unclear about the frequency of lethal or potentially harmful outcomes to the neonate or the gestational diabetic herself, focus is shifted onto intermediate outcomes such as macrosomia or biochemical changes in the fetus. But the actual impact of these intermediate outcomes on the neonatal morbidity is still unknown.

F. MANAGEMENT OF GDM

Management Rationale

The purpose in managing the pregnant diabetic is to normalize the level of blood glucose to the level of a non diabetic individual with the premise that euglycemia will optimize the pregnancy outcome.

Therapeutic Strategy

Treatment is two-pronged and includes increased fetal surveillance as well as glycemic control. The relative independent impact of each modality of the therapeutic strategy on the overall prognosis is difficult to determine.
The two arms of treatment as practiced today are:

I Metabolic Control
II Fetal Surveillance

I Metabolic Control:

The Second International Workshop-Conference[14] on GDM in 1985 recommended that, once diagnosed, women should first receive dietary therapy.

Pregnant women without persistent fasting hyperglycemia (class A_1) but with an abnormal OGTT, are treated typically by diet al.one. The suggested kilo calorie level ranges between 25-30 kcal/kg of the desired body weight during the first trimester and is about 30 kcal/kg during the second and third trimesters of pregnancy. Pregnant diabetic women who exercise regularly or who are moderately physically active may require 35 kcal/kg of the desired body weight to achieve the recommended weight gain. The meal schedule must take into consideration patient's lifestyle, food preferences, ethnic background, pre-pregnancy weight, and weight gained during pregnancy.

The diet should be based on the patient's ideal body weight. Controversy exists about the best intake for those who are overweight[130 131]. Reports of infants with low IQs being born to healthy women who developed ketonuria during pregnancy[117] have raised concern about reducing the intake of calories or carbohydrates. However, the study by Churchill et al.[132] has been widely disputed due to the methodology used and the question of chorioamnionitis causing intellectual impairment. And also more recently in 1991, Rizzo et al.[133] found no relationship between maternal hypoglycemia and intellectual function of the offspring.

Recommended weight gain on the basis of pre-pregnancy BMI

Table 2.5

BMI	Recommended Wt Gain
< 19.8 kg/m^2	12.7-18 kg
19.8-26 kg/m^2	11.3-15.5 kg
26-29 kg/m^2	6.8-11.3 kg
> 29 kg/m^2	At least 7 kg

Weight Gains of <1 or >3 kg/month for normal weight women should be evaluated. According to the 1990 workshop, exercise prescriptions, should be individualized and be under careful supervision.

Participants at the Workshop-Conference (1991) observed that although insulin is now recommended widely when standard dietary management does not consistently maintain normal fasting glucose of 5.5 mmol/l or less, or the 2-hour postprandial glucose of less than 6.5 mmol/l, or both; such therapy requires additional cost-benefit studies.

SUMMARY OF MANAGEMENT

Goals

- Maintain normoglycemia
- Avoid ketonuria
- Ensure appropriate maternal weight gain
- Achieve optimal fetal growth.

Methods

- Control type, amount and distribution of carbohydrates in diet
- Eat small, frequent meals
- Monitor capillary glucose levels
- Administer insulin if glucose levels before meals > 5.5 mmol/l or two-hour after meals > 6.5 mmol/l
- Ensure appropriate fetal surveillance

During the treatment, testing is done each day before and two-hour after breakfast, lunch and dinner. Target glucose levels are less than 5.5 mmol/l fasting and less than 6.5 mmol/l two-hours after meals.

Insulin Therapy

Most diabetic clinics add insulin only if, despite compliance with diet, blood glucose levels are exceeded on more than two occasions. The American College of Obstetrics and Gynecology recommends that insulin be initiated to patients when fasting plasma glucose is >5.5mmol/l or when the postprandial glucose is >6.5mmol/l[14 28]. A recent national survey[134] in America showed that although 50% of the care-providers followed the American College recommendations, another 50% used either higher or lower threshold criteria. The recommended use of >6.5mmol/l for postprandial glucose was followed by only 22% of those surveyed, whereas almost 80% resorted to various threshold levels unsubstantiated by research. What needs to be ascertained is whether any particular treatment strategy has beneficial effect on the morbidity.

Insulin Administration

Insulin administration should always be synchronized with patient's meal patterns. The management of GDM is similar to that of pregestational diabetes and insulin is administered in regimens similar to those in patients with pre-existing diabetes.

The insulin dose is calculated based on current weight at initiation of therapy prescribing 0.7U insulin per kilogram of body weight. The standard formula for the insulin dose is prescribed as two thirds of all insulin in the morning and one third in the evening. If the primary abnormality is a high fasting glucose value, then the use of NPH or Lente at bedtime may suffice. If the two-hour postprandial glucose values are elevated, then short-acting insulin given before each meal may be required. A typical starting regimen is 8 units regular human insulin prior to breakfast and 6 units prior to lunch and dinner.

Exercise Therapy

Although exercise has been recognized since ancient times as a therapeutic strategy for obesity, but it is only recently that it has been recognized that exercise does increase the sensitivity of insulin[135]. The exact mechanism whereby exercise benefits glucose tolerance is not known. However, it has been suggested that possibly with exercise there is an increased capacity for glucose transport into muscle and adipose tissue in response to insulin. An increase in capillary density in muscle may play a role.

The routine use of exercise as a treatment for gestational diabetes is not yet standard practice, however preliminary work in this field by the researchers warrants in-depth studies.

Monitoring Blood Glucose

Self monitoring of blood glucose (SMBG) is widely used in IDDM. Self-monitoring is mostly done with the help of reflectance glucometers with or without memory. Glucometers are standardized against laboratory values from time to time. All systems depend on glucose-oxidase calorimetric reaction between a drop of patient's blood and a reagent strip. All meters are battery operated and use solid-state electronics. The effective concentration range depends on the system but generally covers the clinically relevant range. Properly used, the available technology could be sufficiently accurate for long-term patient management. However, all available systems are highly dependent on user skills and the efficiency of the therapeutic regimes instituted remains dependent upon:

- slight differences between readings of different meters
- inter-individual differences of readings
- intra-individual differences of readings
- quality of training provided

With current systems, SMBG measurements are within 15% of the results of the reference lab values. The cost of blood glucose monitoring is a concern. It costs about $175 to a patient performing four tests a day throughout the last trimester of pregnancy[136].

The benefit of routine use of self monitoring glucometers in GDM may be questioned, except in more severe cases[136].

II Obstetrical Management And Fetal Surveillance

In most patients with GDM with well controlled blood glucose levels, spontaneous vaginal delivery is expected. Obstetrical management need not differ from that of normal pregnancy. Ultrasound evaluation may provide some clue to fetal weight and abdominal circumference.

Intrapartum Management

Intrapartum management of women with gestational diabetes is only a little different from that of the normoglycemic pregnant women. In patients with estimated fetal weight between 4000-4500g, management should be individualized based on the size of the pelvis and the patient's previous obstetric history. In addition, the use of mid pelvic operative delivery should be discouraged in patients with suspected macrosomia.

Unless excellent glycemic control has been achieved throughout the pregnancy with diet management, blood glucose should be checked every 1 or 2 hours during labour and short-acting insulin given to maintain a reasonable level of control. Insulin is discontinued at the time of delivery.

Postpartum Management

Almost all patients (98%) with GDM resume normal glucose metabolism after delivery[137]. It can be confirmed by capillary glucose testing in the hospital. Normally, the blood glucose needs to be checked only once or twice postpartum to ensure that it is at an acceptable level. At six weeks postpartum it is worthwhile to have a glucose tolerance test carried out using the 75-gram 2-hour OGTT. About 1% of patients manifest an abnormality in glucose tolerance at this postpartum visit.

As per recommendations of the Second International Workshop-Conference, these women should be followed post-partum at periodic intervals in order to detect diabetes early in its course, particularly in preparation for any future pregnancy.

G. SPECULATION

Despite documented excellent glucose control by some of the treatment modalities, there remains a group of gestational diabetics (glycemia controlled) who have a higher rate of macrosomia than that of the non-diabetic pregnancy[11 138]. Explanations for this apparent contradiction include the possibilities that either hyperglycemia by itself is not the major factor related to macrosomia or that the degree of glycemic control reported in most studies is subject to significant errors.

H. RISK OF OVERT DIABETES IN LATER YEARS

Women whose glucose value exceeded the mean by three standard deviations had a 60% chance of becoming diabetic in the 8-year follow up period. O'Sullivan, in a long-term study of the outcome of women with gestational diabetes has shown the development of overt diabetes beyond 20 years following pregnancy to be as high as 20%, and 50% had impaired glucose tolerance[85].

CHAPTER 2

REVIEW OF THE LITERATURE

2.3

MATERNAL ANTHROPOMETRY

A. INTRODUCTION

Maternal anthropometric parameters may influence pregnancy outcomes and perinatal morbidity. Their application for screening, monitoring or evaluating risk for adverse maternal outcomes has been limited, though specific indicators have been found to be related to some specific outcomes; such as maternal height for risk of cephalopelvic disproportion, increased pre-pregnancy weight to the risk of pre-eclampsia. Pre-pregnancy weight and weight gain during pregnancy, both have been shown to be related to birth weight and infant mortality[140] [141].

I Pre-pregnancy Weight

Experts at the National Institutes of Health Conference in 1985 agreed that a body weight of 20% or more above desirable weight constitutes an established health hazard[142]. As degree of obesity is a continuum, any definition of obesity must be arbitrary and related to a standard of normality. Both maternal pre-pregnancy weight and weight gain during pregnancy, independently influence newborn weight. However, subjects exceeding 135% of the desirable weight may give birth to heavier babies whose weights may relatively be unaffected by a wide range of maternal weight gains (0-15 kg)[143].

Pathophysiology

Maternal obesity intensifies the insulin resistance already present in late pregnancy and probably also heightens plasma fuel disturbances in the pregnant women. Both basal and carbohydrate-stimulated insulin secretion are increased in obesity[103] [144] which are reversible to some extent with weight loss[104] [145]. Some speculate that the greatly expanded adipose tissue stores of severely obese gravid individuals provide enough substrate to the fetus to promote development of a heavier baby even in the face of reduced food intake and little or no gestational weight gain.

II Body Mass Index (BMI)(kg/m^2)

Body mass index (BMI) is a ratio of weight disproportionately weighted by height and is highly correlated with weight itself. BMI equivalent of a relative weight of 100% is 22.7 kg/m^2 for men and 22.4 kg/m^2 for women[146 147]. BMI corresponding to acceptable normal weight for women ranges between 19.1 to 27.30. Intervention is indicated at levels of 25.8 or more if there is a family history or risk factors complicated by obesity such as history of GDM, birth of a LGA baby, hypertension, hypertriglyceridemia or hyper-cholestrolemia[142].

Although BMI estimates total body mass rather than fat mass, it correlates highly with the amount of body fat[148]. Medical literature suggests that maternal body mass index is superior to weight alone, for the prediction of morbidity and mortality in non-pregnant populations[148 149] whereas in pregnant women, body weight is comparable to BMI for the prediction of key adverse, weight-associated outcomes.

The main advantages of the use of BMI over absolute body weight are that it is a self-contained calculated ratio which requires no reference tables. Secondly, it is a convenient indicator for comparisons between studies internationally.

Limitation of the use of BMI is that although it correlates with the percent of fat, it does not distinguish between various body components such as muscle, retained water and fat.

B. Relationship Of Obesity With GDM

It is well recognized that obesity causes marked insulin resistance and about 30-50% of gestational diabetic patients are obese. Thus the insulin resistance of obesity compounded by the insulin resistance of GDM pregnancy results in marked glucose intolerance. Gestational diabetes correlates better with BMI than with weight alone[57]; presumably because insulin resistance is more a function of the body fat content than of absolute weight.

C. Management Strategy

Nutritional counseling is the cornerstone of the management of all women with obesity as well as/or with GDM and is based on the standard recommendations for a nutritious diet for pregnant women. Calorie restriction and weight reduction improve insulin sensitivity and insulin binding in obese and gestational diabetic women. Diet can enhance insulin sensitivity in healthy women via the post receptor steps of insulin action taking about 2-3 weeks[150]. Individualization of diet depending on body weight is recommended. An inverse relationship between pre-pregnancy body weight and average weight gain during pregnancy is considered appropriate with a minimum increase of 7kg recommended for the very obese (BMI>29kg/m^2) and up to 18kg for those who are underweight (BMI<19.8kg/m^2) (refer table 2.5 above).

CHAPTER 3

PATIENTS & METHODS

SUBJECT SELECTION AND METHODOLOGY

A. PATIENT POOL

The study population consisted of 1000 women, 857 from the Royal Alexandra and 143 from the Grey Nuns Hospital of Edmonton, and their newborns. They were delivered from January 1993 through December 1993. Royal Alexandra is a tertiary-care hospital with facilities of an intensive care unit. Since we included only term, healthy newborns into our study, (see inclusion/exclusion criteria) the study samples were not dissimilar in spite of being from two different sources.

It was an observational study with cases and controls in the ratio of approximately 1:4. Cases were term babies (≥36 weeks) with bwt ≥4000g (n=209) and controls were term babies with bwt <4000g (n=791).

We had a sufficiently large pool of patients from which to collect our study sample. Factors responsible for the large pool were:

1. Average number of deliveries at the Royal Alexandra and the Grey Nuns hospitals together are more than 7000 per year.

2. One of the inclusion criteria for the subjects was the performance of a 50 g GCT (screen test) at 24-28 weeks of gestation. Although obstetricians are expected to carry out this test routinely; a feasibility study showed that the screen was being ordered in about 70% of patients only. Obstetricians at the participating hospitals were contacted and urged to carry out the test routinely as per the existing guidelines in Canada and were also updated about the study at various 'business meetings'. A compliance rate of almost 80% was achieved by the time patient recruitment started. Compliance further increased as the study progressed.

3. Patient participation in the study was excellent as there were no invasive or painful procedures involved in data collection.

B. AVOIDING BIAS

Strategies for minimizing random errors and biases have been applied in both the design and the analysis phase of research. The following table explains strategies involved in avoiding bias due to random, systematic or measurement error during the design or the execution phase of the study.

Biases and Checks

Table 3.1

Error due to	Strategy applied	Check
I. Random Bias		
	1. Adequate Sample size	Interpret p-value
	2. Standardizing the measurement methods	Maintain Operations Manual
	3. Checking inter-observer and intraobserver variability periodically	Maintain correlation coefficient of >0.75
II. Systematic Bias		
	1. Check external validity	Check consistency with other studies using different designs and methods of analysis
	2. Check internal validity	Analyze by more than one technique Explain inconsistency in results, if any
III. Measurement Bias		
	Use of data that was recorded before the outcome occurred	No chance of recall or investigator-related bias

C. DESIGN OF THE STUDY

The study was designed to explore causal-inference of association between the predictors of macrosomia and the outcome of macrosomia.

The study design was appropriate for the proposed objective of finding the relative importance of predictors of macrosomia and predictors of disproportionate growth in newborns. Cases were macrosomic babies with birthweight $\geq$4000g and controls were non-macrosomic babies with birthweight <4000g. Subsequent to recruitment, a category of 'large for gestational age' newborns (>90th percentile by age and gender) was selected out of the total of 1000 subjects, using tables by Arbuckle[30] et al.. Macrosomia was analyzed by both the 'absolute birthweight' criteria and by the 'gender specific weight by gestational age' criteria.

D. SELECTION OF THE SUBJECTS

I. Initial selection of potential cases and controls was done from the delivery records at the participating hospitals within 24-48 hours after delivery. (Because of the early-discharge program in effect at the participating hospitals, most of the patients left hospital within 48 hrs of delivery).

Inclusion Criteria at initial selection

-singleton pregnancy having delivered more than 24 hours ago. 24 hours are allowed for resolution of edema on newborn's head or soft tissue.
-50 g GCT performed
-term pregnancy. Term pregnancy being defined as 36 completed weeks of gestation. Confirmed expected date of confinement by last menstrual period (LMP) or by ultrasound measurements prior to 20 weeks of gestation.
-no fetal or newborn congenital anomalies

Exclusion Criteria at entry

-incomplete record on 50 g GCT result
-multiple pregnancy
-pre-term delivery

-pre-gestational diabetes mellitus in the mother

-significant maternal pre-existing medical conditions that are known to have an effect on fetal growth e. g. pre-eclampsia, hypertensive disorder, collagen and auto-immune disorders.

- history of medication use that is known or thought to alter growth

-evidence of congenital infection or congenital abnormality

II. Selection of subjects complying with specific inclusion criteria after review of medical records.

Specific Inclusion Criteria

-50 g oral glucose challenge test (GCT) done between 24-28 weeks gestation followed by a 3-hour OGTT for those who were positive on GCT. The cut-off level for a positive GCT was $\geq$7.8mmol/l. Results were interpreted according to the National Diabetes Data Group (NDDG) criteria[111].

III. Approaching women and obtaining consent

Women were approached 24-48 hours after delivery and consent was sought for an interview with the mother and for morphometric measurements of the baby (Appendix III).

E. VARIABLES UNDER INVESTIGATION

Maternal/Paternal

1 Pre-pregnancy weight in kilograms

2 Maternal height in meters

3 Maternal age

4 Weight gain during pregnancy was the difference between weight noted at the time of confinement and the pre-pregnancy weight.

5 Maternal birth weight as <4000g or $\geq$4000g

6 Maternal history of smoking as 5, 10, 15, 20 or more cigarettes per day

7 Expected Date of Delivery by sure dates or confirmed by ultrasound before 20 weeks of gestation

8 Gestational age

9 Previous history of macrosomia as 1, 2, 3..... or more babies with birthweight ≥4000g in the past

10 Parity

11 Value of the 50-g GCT

12 Values of the100-g OGTT: Fasting, 1hr, 2hr, 3hr

13 Ethnicity

14 Paternal weight and height for calculating BMI

15 For GDM subjects: GDM subjects received standard therapy.
(a) Post treatment average of the fasting glucose values and average of the post-meal glucose values as recorded by home glucose monitoring
(b) compliance with the treatment plan

16 Body Mass Index (BMI): calculated by
weight in kilograms/height in $meters^2$

Neonatal

1 Birthweight

2 Crown-Heel Length

3 Head Circumference

4 Mid-Arm Circumference

5 Abdominal Circumference

6 Sex

7 Ponderal Index(PI): It was calculated using formula:
weight in gramsX100/height in cms^3

8 Mid-arm circumference:Head circumference (MAC:HC)

9 Abdominal circumference:Head circumference (AC:HC)

Choice Of The Dependent Variable

Macrosomia was analyzed as a dependent variable. Macrosomia was defined not only in terms of 'absolute birthweight' (i.e. ≥4000g) but also as 'large for gestational age' (>90th percentile) by gender; thus removing any error due to failure to consider gestational age and gender.

Choice Of The Independent Variables

In the list of potential predictors of macrosomia, 'gestational diabetes intermediate' (GDI: GCT+ and OGTT-) was examined as an independent variable, separate from the non-GDM group. GCT was $\geq$7.8mmol/l in this GDI group of subjects with '0' or 'one' abnormal value on OGTT. Two abnormal values on OGTT as per NDDG criteria is classified as a GDM. GDI group was also examined for any synergistic effect with maternal obesity in the multivariate model; just as treated GDM was examined for any synergistic effect with maternal obesity.

Studies in the past have not examined 'gestational diabetes intermediate' group (GDI) in a multivariate model. The importance of this intermediate group lies in the fact that at some centers this group of patients is managed by therapeutic interventions for glucose intolerance. Therefore, it could be considered as an 'untreated'; albeit mild form of glucose intolerance, removing partly the possible masking effect of treatment present in the GDM group.

F. DEFINITIONS OF THE VARIABLES USED

1. Maternal Obesity

By Pre-pregnancy Weight

mild obesity	wt 90-120 kgs
moderate obesity	wt $\geq$ 120 kgs

By Body Mass Index

mild obesity	BMI 28-30 kg/m^2
moderate obesity	BMI $\geq$ 30 kg/m^2

Pre-pregnancy weight and height were noted down from the pre-natal chart record. Weight was recorded on the first pre-natal visit within the first trimester.

2. 50 g oral glucose challenge (GCT):

The 50-gram glucose screen consists of women ingesting 50-grams of a glucose drink and then measuring their plasma glucose level 1-hour later. There is no dietary preparation required for this test and no restrictions as to the time of

the day. Women with values of plasma glucose in excess of 7.8 mm/dl are recommended to undergo a formal 3-hour oral glucose tolerance test.
A random chart review as part of the feasibility study, at both the contributing hospitals revealed that approximately 80% of the prenatal patients were appropriately screened at 24- 28 weeks of gestation.

3. Oral Glucose Tolerance Test (OGTT)

For the OGT Test, methodology is as described in the introduction section. The glucose oxidase/hexokinase method was used for biochemical analysis.

Diagnosis of gestational diabetes

Diagnosis of GDM was made according to criteria of the National Diabetes Data Group (NDDG)[111]. It was confirmed that all relevant labs serving clinicians in these two hospitals used the same diagnostic criteria.
Results of the test were considered to be diagnostic of GDM when any two of the following values were exceeded:

fasting plasma glucose level of	5.8mmol/l
1 hour plasma glucose level of	10.6mmol/l
2 hour plasma glucose level of	9.2mmol/l
3 hour plasma glucose level of	8.1mmol/l

Once diagnosed as GDM, subjects received standard therapy at respective diabetic clinics. Letters of collaboration from the Internists managing these patients at the participating hospitals are attached (Appendix V)

4. Gestational Age

Gestational age was coded as three categories for the multivariate analysis, as: ≤40 weeks, 40 to 42 weeks and >42 weeks.

5. History of Macrosomia

Having had one or more babies with birthweight ≥4000g in the past.

6. Parity

The three categories were: nulliparous, para 1, and para ≥2.

7. Ethnicity

Group A	Hispanic & Caucasian

Hispanics were grouped with Caucasians as the number of the former was very small in the population and their was a sizable proportion of intermarriages between the two groups

Group B	Oriental

Included people of Chinese or South-East Asian origin

Group C	Black
Group D	North American Aboriginals
Group E	Others

Included in this group E were women of Indian, Pakistani, Arab and Lebanese origin. These women were combined into a single group, as individually there were few in each group.

8. Smoking

Smoking was coded by the reported number of cigarettes smoked per day during pregnancy by mothers.

code	No of cigarettes smoked per day
I	5
II	10
III	15
IV	20 or more per day

G. PROCEDURES AND INSTRUMENTS

After recruitment into the study, a short interview was arranged with the mother and anthropometric measurements of the newborn were performed. Measurements were done by one of the two investigators.

The following procedures and instruments were used in the study:

1 EXTRACTION OF MEDICAL CHART INFORMATION

Information on mother's pre-pregnancy weight, height, age, expected date of delivery (EDD), weight gain, gestational age, parity, weight gain, values of 50g GCT and 100g OGTT, was obtained from the patient's chart. Information was recorded on structured forms (Appendix I).

Glucose values of 50 g GCT done between 24-28 weeks on all subjects (n=1000) and those of 100 g OGTT done on screen-positive women (n=163) were recorded from the prenatal record sheet. In the case of incomplete record on values of OGTT in the prenatal record sheet, obstetrician's offices were contacted and records completed.

2 PERSONAL INTERVIEW

The personal interview included details of maternal/paternal variables under study, on a structured form (Appendix I).

For those on treatment for gestational diabetes mellitus (n=50), average fasting and post-meal plasma glucose values were recorded from the home glucometer diary. Records of patients not compliant with the treatment plan were also maintained.

3 MEAN PLASMA GLUCOSE VALUES

The following measures of plasma glucose values were utilized for examining the extent of glucose abnormality:

I Maternal plasma glucose values of 50-gram glucose challenge test done between 24-28 weeks for all the 1000 study subjects

II Maternal plasma glucose values of 100-gram OGTT (fasting, 1-hr, 2-hr and 3-hr) for those positive on 50-gram GCT (n=163)

III average of the fasting plasma glucose values tested on home glucose monitor, in GDM subjects on therapy for normalization of the plasma glucose values (n=46).

IV average of the post-prandial plasma glucose values tested on home glucose monitor, in GDM subjects on therapy for normalization of the plasma glucose values (n=46).

The GCT plasma glucose value reflects plasma glucose status of the total population of study subjects in second trimester. The OGTT glucose values reflect the glucose status of all 'screen positive' subjects including GDI group and GDM group of subjects, before any form of therapy is started in the GDM group. The average of the fasting and the average of the post-prandial plasma glucose values reflect the glucose profile among gestational diabetic women undergoing treatment for normalization of plasma glucose.

4 DISTRIBUTION OF SUBJECTS AND NUMBERS (N=1000)

Table 3.2

Characteristics	**Number**
Neonatal	
birthweight ≥4000g	209
birthweight <4000g	791
large for gestational age>90th centile	179
Maternal	
Non-GDM	949
(GCT-)	836
Intermediate (GCT+ & OGTT-)	113
GDM (GCT+ & OGTT+ & received therapy)	50
Prepreg Wt ≥90kg	59
BMI ≥30	112
Smokers vs. Non-smokers	292 versus 708
Previous h/o macrosomia (at least one baby ≥4kg vs. no baby ≥ 4kg)	137 versus 442
Ethnicity:	
Caucasian & Hispanic	759
Oriental	82
Black	18
North American Aboriginal	83
Others	58

5 CODING AND FILING OF DATA

Data was subsequently coded and filed into computer-based program MacIntosh-Excel. There were missing records on OGTT values of three subjects. These subjects were started on treatment of GDM by the internists, either on consideration of their GCT level >7.8mmol/l or due to a positive history of GDM in the previous pregnancy, without getting OGT test done. During analysis of GDM as a group, these subjects were treated as gestational diabetic; whereas during analysis of OGTT values, data on only 47 subjects were available. Among GDM subjects on treatment, data on values of average fasting and average post-prandial were available for 46 subjects only, as 1 subject had misplaced her diary of records.

6 MORPHOMETRIC MEASUREMENTS OF THE BABY

Measurements included :

a. Birthweight in grams, noted down from the delivery record sheet .

b. Crown-heel length was measured to the nearest millimeter with length board. Baby was placed on its right side along the length of calibrated board with head touching fixed end of the board. Baby's back and legs were straightened with one hand and movable foot-end was placed just touching the soles.

c. Head circumference was measured at the largest occipitofrontal diameter and rounded to the nearest 0.25 cm; the largest of three consecutive measurements was used. Disposable paper tape was used for the head, the mid-arm-circumference and the abdominal circumference.

d. Mid-arm circumference is a reflection of muscle and fat stores. Its measurement 24 hours after birth of the baby allows for the resolution of edema caused by labour and delivery. Mid-arm circumference was measured at the mid-point of the upper left arm, which was isolated by measuring the distance between the acromion and olecranon with the arm held in a horizontal position using technique described by Sasanow et al.[82]. Mid-point is easily located in a term infant by identifying a crease in the skin and MAC is measured at this mid-point with the arm held in extension and the hand prone. This measurement was rounded to the nearest 0.25 cm.

e. Abdominal circumference has been reported to be the best fetal biometric parameter that correlates with fetal weight[159]. Since liver is the largest intra-abdominal organ, assessment of AC at the lower level of umbilicus is actually an indirect estimation of the nutritional status of the newborn. Measurement was made with the help of a disposable measuring tape with baby supine and quiet. This measurement was rounded to the nearest 0.25 cm.

7 INTER-INVESTIGATOR CORRELATION COEFFICIENT

Inter-investigator variability of anthropometric measurements has been kept to a minimum by having only two investigators perform all the measurements. Both the investigators recorded anthropometric measurements of five newborns on two separate occasions two weeks apart. The purpose was to establish inter-investigator reliability of measurement. The Pearson's correlations between the two investigators with p<.05 were as follows:

Inter-Investigator Correlation Coefficient

Table 3.3

	Measures	r
1.	Crown-Heel Length	0.85
2.	Head Circumference	0.92
3.	Mid-Arm Circumference	0.95
4.	Abdominal Circumference	0.84

8 MANAGEMENT OF GDM

Gestational diabetes mellitus management was provided by a diabetes team including a physician, a nutritionist and a social worker. The medical treatment at each of the two hospitals was carried out almost exclusively by single internists. The management scheme for the most part was uniform across internists (see appendix IV; letters of support). Women attended the diabetic clinic once every one to two weeks.

The approach emphasized the following features:

euglycemia
normal maternal weight gain
fetal biophysical assessments
anticipated term delivery.

Diet Therapy:

Diet was prescribed based on 25-35 kcal/kg desirable body weight. Recommended weight gain on the basis of pre-pregnancy BMI is shown in table 2.5.

Salient Features of Diet Management

Table 3.4

Meal Plan consists of three meals and three snacks spaced evenly throughout the day. This measure allows maximum use of endogenous insulin
Small frequent meals, at regular intervals
Protein must be included in main meals and the bedtime snack

Average Diet Composition is 50% carbohydrate, 20% protein, and 30% fat. The bedtime snack contains complex carbohydrate and protein to prevent nocturnal hypoglycemia and morning ketonuria.

Caloric Intake depends on basal needs derived from pre-gravid weight, height, age and physical activity.
Additional 150 kcal starting at 20th week

Fiber Content should be increased through whole grains, legumes, and fruits

Starvation Ketosis Ketonuria in the morning indicates starvation ketosis. It can be eliminated with more carbohydrate at bedtime or a small nocturnal snack

Bedtime Snack should contain 20-50 g of carbohydrate and 30 g of protein

Water should be the main source of fluids

Insulin Therapy:

The patients receiving insulin need to be consistent with the timing of meals and food choices, especially the carbohydrate content. Insulin was used only in women who had 20% values of fasting blood glucose (FBG) >5.5 mmol/l and/or those of postprandial blood glucose (PPBG) >6.5 mmol/l on 20% of occasions.

The percentage of women put on insulin therapy last year at the RAH, GDM clinic was 17.5%. The cut-off levels for starting insulin treatment were different at Grey Nuns hospital from RAH. They were FBG >5 mmol/l and PPBG >6 mmol/l for 20% of the values. The percentage of women put on insulin therapy at the Grey Nuns hospital last year was 36%.

Self Monitoring Of Blood Glucose (SMBG):

Monitoring was done in both, the diet only therapy group, and in the insulin and diet therapy group. Home glucose monitoring was carried out four times per day, i.e. once fasting in the morning and thrice 2-hour postprandial i.e. after breakfast, after lunch and after dinner. Women at the RAH used memory based one-touch-II glucometers from Lifescan. Glucometers used at the Grey Nuns hospital did not necessarily have memory. These meters were calibrated with the laboratory values of plasma glucose and were standardized against laboratory values from time to time. Pregnant women attended the diabetic clinic every one or two weeks depending on the level of glycemia maintained.

Obstetrical Interventions:

Recommendations are that preterm induction of labour and delivery should not be considered unless fetal jeopardy is suspected. Sometimes these guidelines are not strictly observed, particularly when a large baby is suspected in the presence of glucose intolerance. I have examined macrosomia using absolute birthweight criteria as well as large-for-gestational age criteria to avoid errors due to non-consideration of gestational age and gender.

9 STATISTICAL METHODS

The initial exploratory analyses were conducted using the following statistical tests:

I Univariate Analyses

a. T-tests to determine differences in means between two groups
b. Pearson's correlation coefficients
d. Chi-square tests to determine differences between proportions

II Multivariate Analyses

Multivariate analytic methods have been used for assessing the independent contribution of predictor variables in this observational study. One of the great advantages of multivariate adjustment technique is the capacity to control the influence of many confounders simultaneously. Another advantage is their use of all the information in continuous variables which is not the case with univariate analysis of discrete variables.

a. Adjustment For Confounding

A mistaken assessment of risk may result from uncontrolled confounding. The study predictor variable, by virtue of its association with some other variable, may appear to elevate or reduce the risk of disease when in fact it has no effect. A related consequence of confounding is that the effect of an exposure may be distorted. In order to make adjustments for the effect of confounders the following techniques were used :

b. Multiple Logistic Regression

This technique was used to fulfill the following purposes:
1) to evaluate dependent variables with a skewed distribution as dichotomous variables

2) to allow for the quantification of the effect of each risk factor while at the same time adjusting for the possible confounding effects of other variables[152] [153]

3) to obtain odds ratios, which can be easily interpreted in terms of risks

The general form for multiple regression models[154] can be expressed as:

$$\text{In}\left(Y/(1-Y)\right) = \text{alpha}+\beta_1X_1+\beta_2X_2+\ldots\ldots\ldots+\beta_kX_k+\text{gamma}_{1\,2}(X_1X_2)+e$$

The logistic model implies that the log odds In ($Y/1-Y$) is a linear function of the variables X_1, ...X_k. For dichotomous dependent variable (e.g. cases and controls), Y is the probability of one of the binary outcomes (e.g. macrosomia) and $Y/1-Y$ is the odds of Y. If the independent variable is binary, the coefficient β is the logarithm of the odds ratio for that variable in relation to the outcome of interest. 'Gamma' represents coefficient of the interaction term between X_1 and X_2. Estimates of the parameters β_i and gamma are made under the assumption that the variables in the model equation either have a scale of measurement or that the representation makes proper allowance for the lack of one.

Discrete variable such as ethnicity does not have an ordinal scale of measurement. Indicator (dummy) variables taking the values 1 or 0 to designate the presence or absence of an attribute are used to represent the effects of such variables in a logistic regression model. The logistic regression procedure in the SAS statistical package allows for the analysis of ordinal response data by fitting a (log odds) parallel lines regression model based on the cumulative probabilities of the response categories[155].

Odds ratios were obtained by maximum likelihood estimation for the dichotomized as well as continuous independent variables. To estimate the actual magnitudes of the parameters or the probabilities of events under the logistic model, maximum likelihood estimation is a better choice as compared to discriminant estimation of logistic parameters. Maximum likelihood estimation does not depend on any 'a priori' assumption of multivariate normality. Furthermore, maximum likelihood generally gives slightly better fit to the logistic model.

Models were examined by the step-wise entry method i.e. independent variables were examined at each step for entry or removal according to the level of statistical significance and this procedure finds the 'best fit' within a specified functional form. The purpose of using this method was to identify only those variables that were significantly associated with the outcome. From the viewpoint of scientific explanation, there are at least three weaknesses in this approach. First, the procedures do not distinguish among associations that are causal, non causal or artifactual (due to some source of study bias). Second, the procedures emphasize formal tests of significance, which are dependent on the size of the study sample. In large studies, variables with trivial effects on the risk of disease may be selected for inclusion in the model because of small p-values, while reverse may be the case in studies of small sample size where important effects may be ignored. Third, stepwise selection procedures are oblivious to causal paths. A variable that is an effect of the disease may get included in a model intended to identify disease risk factors.

Interactions terms were tested only when supported by the theoretical framework.

c. Least squares regression analysis

Least squares regression analysis was used to evaluate outcomes that were measured on a continuous scale e.g. anthropometric measurements. As before, this allowed the quantification of the effect of each risk factor while adjusting for the effects of potential confounders. Each dependent variable was analyzed separately.

10 SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculations were derived from the tables in Hulley and Cummings[156] for 'comparison of proportions' and also from the 'tables for sample size calculations for logistic regression'[157]. Sample size calculations have also been checked with the computer program 'Power'[158] for 'comparison of proportions'. The sample size was adequate for at least a power of 90% with alpha=0.05, two tailed.

The sample size and its statistical power was estimated as follows:

I. By using the z-statistic to compare proportions of dichotomous variables[156] (chi-square test):

With case-control design of the study and predictor variable as maternal obesity (as BMI>30), sample size was calculated using formula:

$$N=\left(Z_{alpha}\sqrt{P(1-P)(1/q_1+1/q_2)}+Z_{\beta}\sqrt{P_1(1-P_1)(1/q_1)+P_2(1-P_2)(1/q_2)}\right)^2 \div (P_1-P_2)^2$$

where,

P_1 represents the proportion of controls with the predictor variable,

i.e. proportion of 'mothers of non-macrosomic babies' with maternal obesity (defined as BMI>30), say 10%.

P_2 represents the proportion of cases with the predictor variable,

i.e. proportion of 'mothers of macrosomic babies' with maternal obesity (defined as BMI>30), say 18%.

q_1= proportion of controls in the study sample i.e. subjects in group 1

q_2= proportion of cases in the study sample i.e. subjects in group 2

N= total number of subjects

$P= q_1P_1+q_2P_2$

z_{alpha}= the standard normal deviate for alpha.

(two tailed, $z_{alpha}=1.96$ when alpha=0.05)

Z_{β} = the standard normal deviate for ß. ($Z_{\beta}=1.282$ when $\beta=0.10$)

For two-tailed level of alpha =0.05, ß=0.10; sample size calculations are as below:

$$N = \left(1.96\sqrt{.12x.88x5.3}+1.282\sqrt{(.18x.82x4)+(.1x.9x1.33)}\right)^2/.0064$$

$$N= (1.47+1.08)^2/.0064=1016$$

In our study, cases and controls were in the ratio of approximately 1:4 and total sample consisted of 1000 subjects.

II. By using t-test to compare means of continuous variables[156] for unequal groups:

Formula: $N=\left((1/q_1+1/q_2)\ S^2\ (z_{alpha}+z_{\beta})^2\right)/E^2$

where,

z_{alpha}= the standard normal deviate for alpha. (two tailed, z_{∞}=1.96 when alpha=0.05)

$Z_{ß}$ = the standard normal deviate for ß. ($Z_{ß}$=1.282 when ß=0.10)

q_1 = proportion of subjects in group 1

q_2 = proportion of subjects in group 2

N = total number of subjects required.

S = standard deviation of the outcome variable

E = Expected effect size

Considering standard deviation of newborn's birthweight of 500g and using the formula as above, we can detect an effect size of 125 g difference in baby's birthweight between the glucose tolerant (GCT -, n=837) and the glucose intolerant (GCT+, n=163) groups of women. As per the distribution of subjects in our study sample, there were 50 GDM subjects and 113 GDI i.e. intermediate subjects. A mean difference in birthweight of approximately 250 g between the GDM and the GDI (GCT + and OGTT -) subjects can be detected using the same formula and parameters (alpha, two-tailed=.05 and power=90%).

III. Using tables[157] for sample size calculations for logistic regression, for a level of significance of alpha=0.05, one tailed, in a model with 10 independent variables; the statistical power to detect an odds ratio at one standard deviation above the mean (r=1.5) of the covariate maternal obesity with P=0.10 (where, P is an overall event proportion of macrosomia) was estimated to be approximately 85%.

Study Sample For Nomograms

At the RAH, from Oct 1 1992 to Sep 30 1993, the percentage of babies ≥36 weeks gestational age weighing ≥4000g was 11.3%.

Our original study sample consisted of 209 macrosomic and 791 non-macrosomic newborns. A random sample of 100 babies out of the 209 macrosomic newborns was created with the help of SPSS/windows program. This random sample was combined with a sample of 790 non-macrosomic newborns making a total of 890 subjects. This assembled group included 790 non-macrosomic and 100 macrosomic newborns resulting in 11.2% rate of macrosomia. This sample represented local, healthy, term, singleton newborns at the RAH and the Grey Nuns hospital between Jan 93 to Dec 93. Nomogram tables of 10th, 50th and 90th percentiles of the three measures of disproportionate fat distribution .e. ponderal index, MAC:HC ratio and AC:HC ratio in the newborns were compiled from this sample of 890 newborns.

11 STATISTICAL PROGRAM USED

Initial data entry and manipulation was done using MacIntosh Excel. Univariate as well as multivariate models were tested using SAS on the mainframe. Graphs and nomograms were plotted on SPSS/windows program.

12 COLLABORATIVE APPROACH

We sought collaboration with the internists managing diabetic clinics and also with the physicians in-charge of obstetrics at both the participating hospitals, regarding uniformity of approach and procedures. Letters of support attached (see Appendix IV & V)

13 ETHICS APPROVAL

Ethics approval for this project was obtained from the Ethics Review Committee at the Royal Alexandra Hospital and the Grey Nuns Hospital. Signed consent forms were obtained from all the participants.

CHAPTER 4

RESULTS I: PREDICTORS OF MACROSOMIA

This section deals with the results of objective I i.e. predictors of macrosomia. Outcome of fetal macrosomia has been examined by both the definitions of macrosomia i.e.

1 absolute birthweight ≥ 4000g

2 large for gestational age >90th percentile, (birthweight weighted by gestational age and sex)

Univariate statistical methods were used as a first step to examine the association of different variables with the outcome of fetal macrosomia. Initial analysis and assumptions based on the theoretical framework led to the final model for testing by the step-wise multiple regression technique.

A. PREDICTORS OF FETAL MACROSOMIA

(i) UNIVARIATE ANALYSIS

1. Comparison Of Maternal/Paternal Characteristics Between Macrosomics And Non-Macrosomics

1a. The average values of the maternal/paternal characteristics measured on continuous scale with macrosomia defined as birthweight ≥4000g and examined by t-test:

Table 4.1

Maternal/Paternal characteristics in macrosomic and non-macrosomic newborns

Variables	Birth wt<4000g (n=791)	Birth wt>4000g (n=209)	p
Pre-pregnancy Weight	62.6 kg	70.1kg	.0001*
Maternal BMI	23.4kg/m^2	25.3kg/m^2	.0001*
Weight Gain	14.3kg	16.9kg	.0001*
Maternal Height	1.63m	1.66m	.0001*
Maternal Age	27.5yrs	27.8yrs	.37(ns)
Paternal BMI	25.4kg/m^2	26kg/m^2	.07(ns)

* statistically significant

Except for maternal age and paternal BMI all the variables examined in table 4.1 are statistically significantly different between the macrosomic and the non-macrosomics.

1b.The average values of the maternal/paternal characteristics measured on continuous scale with macrosomia defined as LGA >90th percentile and examined by t-test:

Table 4.2

Maternal/Paternal characteristics in LGA and non-LGA babies

Variables	Non-LGA (n=821)	LGA (n=179)	p
Prepregnancy Weight	62.8kg	70.6kg	.0001*
Maternal BMI	23.5kg/m^2	25.5kg/m^2	.0001*
Weight Gain	14.5Kg	16.5Kg	0.0001*
Maternal Height	1.63m	1.66m	0.0001*
Maternal Age	27.3yrs	28.3yrs	0.02*
Paternal BMI	25.3kg/m^2	26.3kg/m^2	0.004*

* statistically significant

2. The Relationship Of Birthweight With The Number Of Cigarettes Smoked Per Day

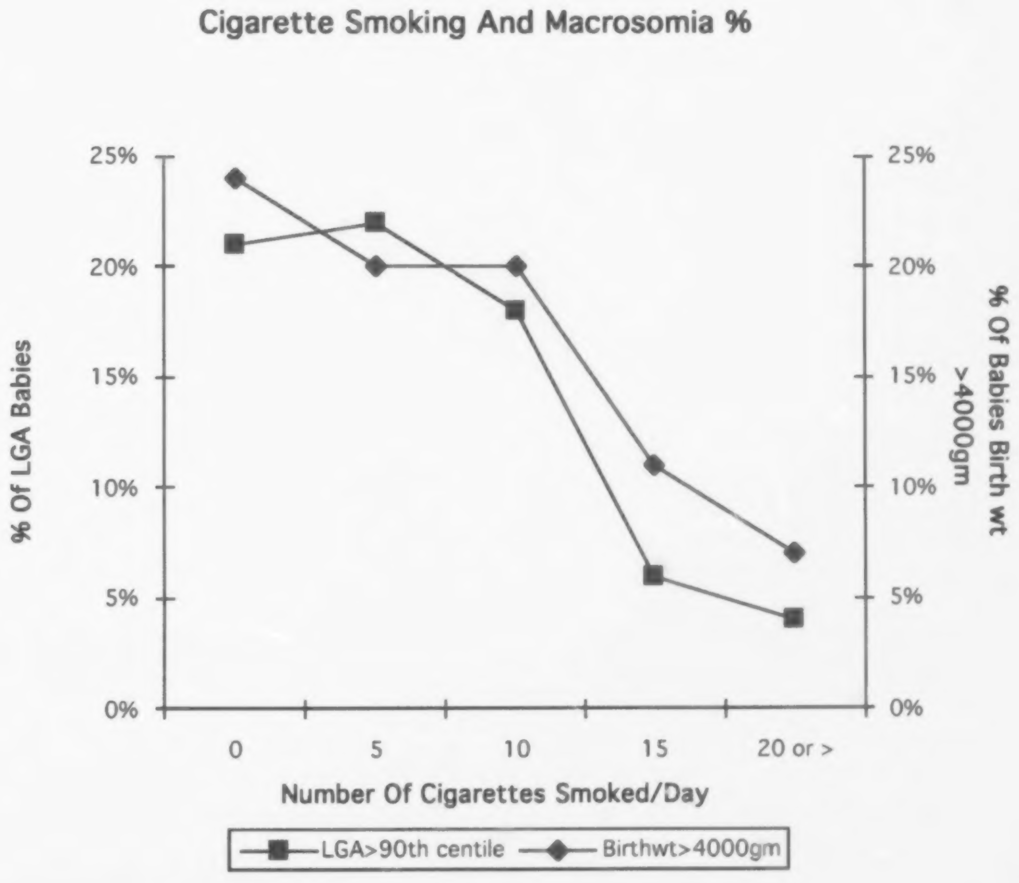
Mothers who smoked cigarettes during the index pregnancy had a lower risk of delivering a macrosomic newborn than a non-smoker. There was a negative correlation between the number of cigarettes smoked per day and the frequency of macrosomia (see table 4.3 and graph 4.1). The proportion of macrosomic babies (birthwt>4000g) was the highest among non-smokers (n= 708) and the percentage of macrosomia was inversely proportional to the number of cigarettes smoked per day. There was a sharp decrease in percentage of macrosomia in subjects who smoked more than 10 cigarettes per day. The effect of cigarette smoking on macrosomia has been further analyzed by the multivariate model.

Table of 'proportion of macrosomia' and number of cigarettes smoked/day
(n=1000)

Table 4.3

Macrosomia defined as	Number of cigarettes smoked/day 0	5	10	15	20 or >
LGA>90th centile	21%	22%	18%	6%	4%
Birthweight>4000g	24%	20%	20%	11%	7%

Fig 4.1



3. The Relationship Of Birthweight With 'Previous History Of Macrosomia'

Table of macrosomia by 'history of macrosomia'

Table 4.4

	No. of macrosomic babies in the past				
Index Pregnancy Incidence of	0	1	2	3 or more	Total N=579 (para$\geq$1)
macrosomia	n=51 11.6%	n=55 51.4%	n=13 56.6%	n=6 85.7%	125
non-macrosomia	n=391 88.4%	n=52 48.6%	n=10 43.4%	n=1 14.3%	454

p-value = 0.000*

There were 579 subjects para $\geq$1 in our study. The table reveals that among para $\geq$1 women (n=579), previous history of macrosomia was highly significantly associated with the outcome of macrosomia in the present pregnancy and the risk increased with increasing number of macrosomic babies delivered in the past. The proportion of macrosomia to non-macrosomia in index pregnancy was 11.6 vs. 88.4 in subjects with no history of macrosomia in the past. The proportion of macrosomia successively increased as the number of macrosomic babies in the past increased i.e. from 51.4% to 85.7%. This effect has been further analyzed by the multivariate model.

(ii) MULTIVARIATE ANALYSIS

Stepwise Multiple Logistic Regression Analysis

Since the study sample was collected in a case-control fashion, some of the variables analyzed did not conform to a normal distribution. This can result in violation of the assumptions related to linear methods on multivariate analysis. Therefore for multivariate analysis, the logistic regression model was applied.

The outcome dimension examined was macrosomia. Macrosomia was analyzed as a dependent, dichotomous variable using both the definitions of macrosomia i.e. absolute weight $\geq$4000g as well as LGA >90th percentile.

Macrosomia was coded as follows:

1= Macrosomia (n=209) or LGA (n=179) 0= Non-Macrosomia or Non-LGA

The following independent variables were analyzed by the logistic regression technique:

a) Previous history of macrosomia

Previous history of macrosomia constitutes delivering at least one baby with absolute birthweight $\geq$4000grams in the past, among $\geq$para 1 women, (n=579).

At least one baby $\geq$4000g birthweight in the past=1

else, no baby $\geq$4000g birthweight in the past=0

b) Maternal Age

1= <17 years

2= >40 years

else, 17-40 years=0

c) Parity

Para 1=1

Para $\geq$2=2

else, Nulliparous=0

d) Smoking

Smoking 5 cigs/day=1

Smoking 10 cigs/day=2

Smoking 15 cigs/day=3

Smoking 20 or more cigs/day=4

else, No smoking=0

e) Pre-pregnancy Weight

As a continuous variable

f) Maternal BMI

As a continuous variable

g) Maternal Height
As a continuous variable

h) Weight Gain
As a continuous variable
i) Gestational Age
40-42 weeks=1
>42 weeks=2
else, <40 weeks=0

j) Maternal Birthweight
≥4000g=1
else, <4000g=0

k) Paternal BMI
As a continuous variable

l) Ethnicity
Oriental=1, Black=2, North American Aboriginal-3, Others=4
else, Hispanic & Caucasian=0

m) Gestational diabetes mellitus
(treated) - GDM

n) Gestational Diabetes Intermediate
- GDI

o) Interaction term: BMIxGD
BMI>30=1
else, BMI<30=0;
GD coded as
GDM=1
GDI=.5
else, Non-GDM=0

p) Interaction term: WtxGD
Pre-preg Wt< 90kg=0
else, Pre-preg Wt=1
GD coded as
GDM=1; GDI=.5; else, Non-GDM=0

Model I: Variables (a) to (p), except for 'the previous history of macrosomia' were included in model I with n=1000. 'The previous history of macrosomia' was excluded from Model I, as its inclusion reduced the sample size to 579 by considering only para ≥ 1 group of women and also that, the nulliparas would get excluded from that model.

The independent variables that satisfied $p<.05$ level of statistical significance, selected in stepwise manner, their odds ratios, standard error, 95% CI and p-values are shown in table 4.5.

Pre-pregnancy weight was found to be most significantly associated with the outcome of macrosomia (birthweight $\geq$4000g) with an odds ratio (OR) of 1.5 per every 15 kg (1 std dev) increase in maternal weight. By this OR, a woman weighing 120 kg before pregnancy was at 5 times the risk of delivering a macrosomic baby than an average weight (average wt of women weighing <90 kg) woman weighing 61 kg; whereas one weighing 105 kg was at 3.4 times the risk.

The second factor to enter the model was maternal weight gain during pregnancy. The odds ratio states that the risk of macrosomia increased by 1.7 times for every 7 kg (1 std dev.) increase in weight gain above the mean value of 15 kg.

Maternal history of smoking during pregnancy was negatively correlated with macrosomia. With each 5 additional cigarettes smoked per day, the risk of delivering a macrosomic baby was reduced by 1.4 times. A woman smoking 20 cigarettes a day was 3 times less likely to have a big baby than a woman smoking 5 cigarettes per day and 4 times less likely than a non-smoker.

A multiparous (para≥2) woman was 2.3 times more likely to have a macrosomic baby than a primigravida.

A male baby was twice as likely to be a macrosomic than a female baby. Similarly, a baby with gestational age ≥40 weeks was at double the risk of being a macrosomic than the one <40 weeks gestation at term.

Odds Ratios (Macrosomia vs. Non-Macrosomia) and p-values

(macrosomia as birthweight ≥4000g)

n=1000

Table 4.5

Variables	OR	SE	95%CI	Multivariate p-value	Univariate p-value
Pre-Pregnancy Weight	1.5 per 15kg	.005	(1.3-1.8)	.0001	.0001
Weight Gain	1.7 per 7kg	.013	(1.67-1.78)	.0001	.0001
Maternal smoking	0.70 per 5 cigs per day	.076	(.6-.8)	.0001	.000
Parity (multi vs. nulli)	2.3	.106	(1.5-3.4)	.0001	.001
Male sex	2.0	.077	(1.4-2.8)	.0001	.000
Gestational Age (≥40 wks vs. <40 wks)	2.0	.173	(1.4-2.7)	.0001	.0001
North American Aboriginal	2.9	.303	(1.6-5.3)	.0004	.000
Maternal birthwt (<4kg vs. ≥4kg)	2.2	.249	(1.4-3.6)	.001	.000
Maternal Height	1.3 per 7 cm	1.34	(1.03-1.5)	.008	.0001
Maternal Age (<17yrs vs. 17-40 yrs)	2.8	.48	(1.1-7.0)	.03	.09
GDI	1.6	.255	(.99-2.7)	.051	.12

OR: odds ratio; SE: standard error; 95% CI: 95% confidence interval for OR; p-value: statistically significant probability

Among different ethnic groups, North American Aboriginal women were about 3 times more likely than the Caucasian+Hispanic women to have a macrosomic baby. Women included under the 'Other' category have been shown to have fewer macrosomic babies (OR 0.5) than the Caucasian+Hispanic group of women at p-value of 0.08 (refer table 4.6).

A woman who was macrosomic at birth was more than twice as likely to produce a macrosomic baby than the one who was of average weight.

It was interesting to find that young mothers <17 years of age had 2.8 times the risk of macrosomia than the other age groups, though there was a wide 95% CI (1.1-7.0).

Maternal height also contributed towards macrosomia. Each 7 cms difference in height from a mean maternal height of 164 cms affected the outcome by a factor of 1.3.

Gestational Diabetes Intermediate (GDI) was the last variable to enter the model at p=.051. By univariate analysis, GDI was not found to be statistically significant for the development of macrosomia (p=.12). In table 4.5, the OR of 1.6 had 95% CI ranging from .99 to 2.7, thereby crossing value of 1.

In model with both, the pre-pregnancy weight and the maternal BMI as continuous independent variables, only pre-pregnancy weight entered at p<.05. Not surprisingly, maternal BMI entered in place of pre-pregnancy weight when pre-pregnancy weight was excluded from step-wise regression model. Since there is a high degree of correlation between pre-pregnancy weight and BMI, maternal prepreg wt might be more predictive than BMI to have entered the model for outcome of macrosomia.

Variables that did not enter at p<.05 level of significance in model I are shown in table 4.6. The interaction terms of BMIxgd and wtxgd were not found to have any association with the outcome of macrosomia in model I. Effect due to interactions has been further explored on page 81.

Variables Not In The Model

Table 4.6

Variable	Chi-Square Score	Pr> Chi-Square
Ethnicity (Other)	0.63	0.08
Maternal Age (other than <17yrs)	0.55	0.46
Pre-preg BMI	0.09	0.77
Ethnicity (Oriental)	1.11	0.30
GDM	0.02	0.89
BMIxGDM	0.06	0.80
WtxGDM	0.61	0.43

Model II: In this model (n=1000), macrosomia was defined as large for gestational age (LGA) at >90th percentile by gender (n=179). Table 4.7 shows the order of the stepwise selection of variables, their ORs, 95%CI and p-values.

Odds ratios (Macrosomia vs. Non-Macrosomia) and p-values

(macrosomia as LGA >90th centile)

n=1000

Table 4.7

Variables	OR	SE	95%CI	Multivariate p-value	Univariate p-value
Pre-Pregnancy Weight	1.57 per 15 kg	.005	(1.35-1.8)	.0001	.0001
Weight Gain	1.56 per 7 kg	.012	(1.3-1.86)	.0001	.0001
Maternal Smoking	.66 per 5 cigs per day	.087	(.56-.78)	.0001	.000
Parity (multi vs. nulli)	2.3	.111	(1.5-3.5)	.0001	.001
North American Aboriginal	2.8	.303	(1.5-5.0)	.0007	.000
Maternal Birthweight (<4kg vs. ≥4kg)	2.1	.25	(1.3-3.5)	.0024	.05
Maternal Height	1.3 per 7 cm	1.36	(1.04-1.5)	.02	.0001
GDI	1.7	.254	(1.3-2.2)	.03	.03

OR: odds ratio; SE: standard error; 95% CI: 95% confidence interval for OR; p-value: statistically significance of probability.

A closer look at the table reveals that the order of entry of the independent variables, their OR values as well as the 95% CI are similar to the previous model. Gestational age and gender did not enter this model due to obvious reasons. GDI was statistically significant at p<.05 by univariate as well as multivariate technique.

Results of Model II reinforce the results found by Model I.

Model III: By including 'previous history of macrosomia' into the model, sample size was reduced to 579, since nulliparous women were excluded from the sample. The order of entry of variables into the model changed substantially with 'previous history of macrosomia' included. Table 4.8 highlights a strong association between development of macrosomia and previous history of macrosomia, with an OR of 9. Odds ratio for all the rest of the variables in this model was close to OR by the first two models.

It seems that the previous history of macrosomia takes into account all the effect due to the maternal physical or metabolic characteristics, therefore neither pre-preg weight/BMI nor any of the levels of glucose tolerance entered the model at p<.05 level of significance.

Odds ratios (Macrosomia Vs Non-Macrosomia) and p-values

(macrosomia defined as large for gestational age >90th centile)

n=579

Table 4.8

	ß	SE	OR	95%CI	p-value
Previous history of macrosomia	**2.2**	**.23**	**9**	**(5.8-14.1)**	**0.0001**
Maternal smoking	**-.43**	**.11**	**.65**	**(.52-.81)**	**0.0001**
Maternal ht	**5.7**	**1.76**	**1.5** **per 7 cm**	**(1.2-1.9)**	**0.0012**
Weight gain	**.044**	**.02**	**1.4** **per 7 kg**	**(1 -1.8)**	**0.015**
Maternal birth weight	**.803**	**.36**	**2.2**	**(1.1-4.5)**	**0.02**

ß: coefficient or parameter estimate; OR: odds ratio; SE: standard error; 95% CI: 95% confidence interval for OR; p-value: statistically significant probability

The variables that did not meet the 0.05 significance level of entry are as in table 4.9:

Variable not in model III

Table 4.9

Variable	Score Chi-Square	Pr> Chi-Square
GDM	3.2	0.07
North American Aboriginal	3.2	0.07
Maternal BMI	2.7	0.10
Maternal Pre-preg weight	2.4	0.12
Male sex	0.75	0.40
Maternal Age (>17yrs)	0.66	0.40
WtxGDM	0.22	0.64
Ethnicity (Other)	0.03	0.87
Parity	0.03	0.87
BMIxGDM	0.02	0.88
Ethnicity (Oriental)	0.02	0.89
Gestational Age	0.001	0.90

B. GLUCOSE INTOLERANCE, MATERNAL OBESITY AND MACROSOMIA

1. Correlation Of Maternal Pre-Pregnancy Weight And Body Mass Index With Levels Of Glucose Tolerance

The three levels of glucose tolerance considered were:

Group I	GCT - and OGTT -	Non-GDM
Group II	GCT + and OGTT -	GDI
Group III	GCT + and OGTT +	GDM (treated)

Percentages of women with ≥30 BMI or ≥90 kg prepreg-wt among the three levels of glucose tolerance

Table 4.10

	Non-GDM	GDI	GDM	p-value
BMI ≥30	**10.2%**	**12.4%**	**25.5%**	**.003***
BMI <30	89.8%	87.6%	74.5%	
Pre-preg Wt≥90kg	**5.1%**	**7.1%**	**15.7%**	**.007***
Pre-preg Wt<90kg	94.9%	92.9%	84.3%	

* statistically significant

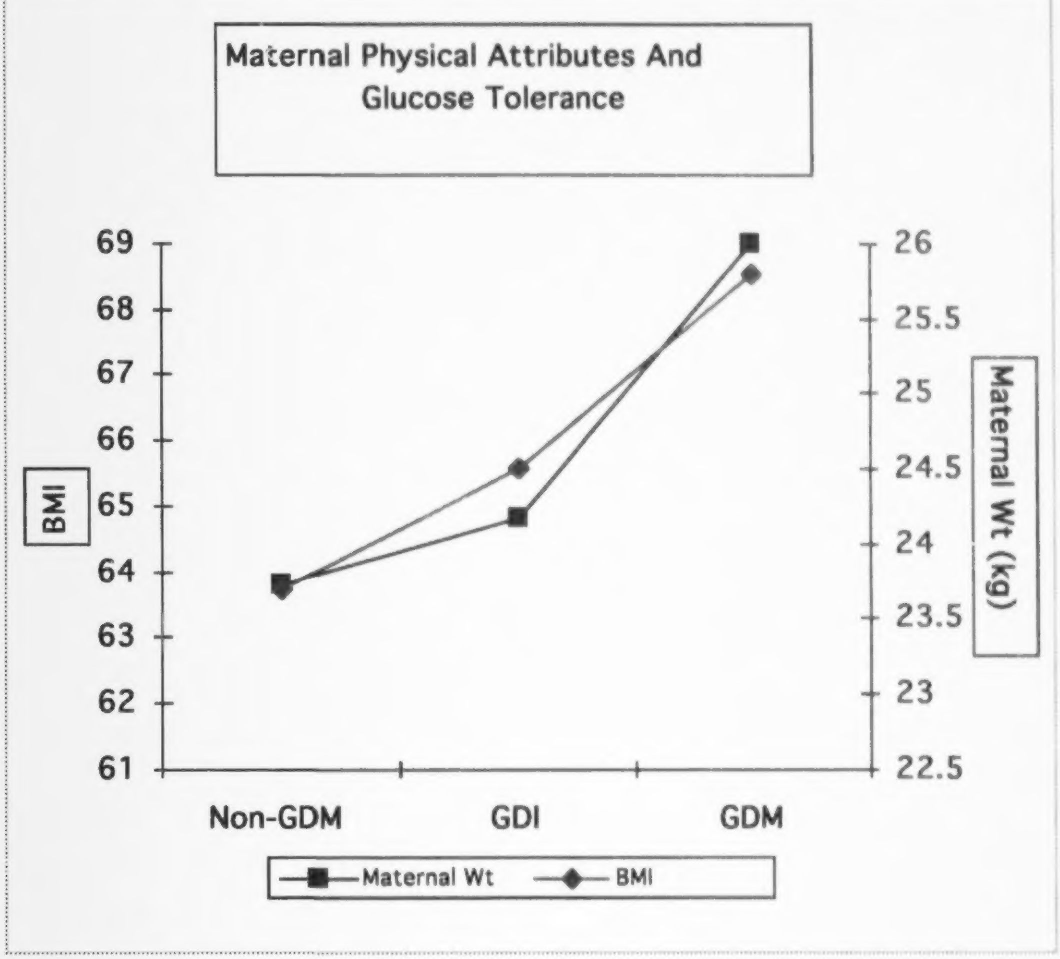
Average values of maternal pre-pregnancy weight and BMI within the levels of glucose tolerance

Table 4.11

	Non-GDM	GDI	GDM
Maternal Wt	63.8kg	64.8kg	69kg
Maternal BMI	23.7	24.5	25.8

On plotting the maternal prepreg-wt and BMI values (table 4.11) with the three levels of glucose tolerance (fig 4.2), we found that the level of glucose intolerance increases with increasing maternal morphometric measures like BMI and pre-pregnancy wt i.e. obese women were prone to glucose intolerance.

Graph 42


Maternal Physical Attributes And Glucose Tolerance
69
68
67
66
65
64
63
62
61
BMI
26
25.5
25
24.5
24
23.5
23
22.5
Maternal Wt (kg)
Non-GDM
GDI
GDM
Maternal Wt
BMI

2. Relationship Of Glucose Intolerance With Macrosomia With Or Without Maternal Obesity

Glucose intolerance in maternal plasma was analyzed for correlation with macrosomia by the univariate as well as the multivariate methods. We examined all three levels of glucose tolerance in non-obese and obese mothers.

Percentage of macrosomic babies in three levels of glucose tolerance
Non-Obese(BMI<30)
(n=888)

Table 4.12

Macrosomia vs. Non-macro	Non-GDM	GDI	GDM	p
Bwt≥4000g	**18.9%**	**26.3%**	**18.4%**	**.22**
Bwt<4000g	81.1%	73.7%	81.6%	
LGA>90centile	**15.3%**	**24.2%**	**21.1%**	**.06**
AGA	84.7%	75.8%	78.9%	

p-value statistically not significant

Among the non-obese women, group-wise comparison (based on levels of glucose tolerance) for proportion of macrosomic babies showed that none of the differences between the groups reached statistical significance, although the proportion of macrosomic babies in GDI subgroup was greater than in the other two subgroups and p-value for LGA group was .06.

Percentage of macrosomic babies in three levels of glucose tolerance
Obese (BMI≥30)
(n=112)

Table 4.13

Macrosomia vs. Non-macro	Non-GDM	GDI	GDM	p
Bwt≥4000g	**31.8%**	**28.6%**	**23.1%**	**.808**
Bwt<4000g	68.2%	71.4%	76.98%	
LGA>90 centile	**29.4%**	**28.6%**	**23.1%**	**.895**
AGA	70.6%	71.4%	76.9%	

p-value statistically not significant

Again in the group of obese women, there were no statistically significant differences in the percentage of macrosomic babies in the three levels of glucose tolerance. It was clearly evident that the proportions of macrosomic babies were greater in the obese group than in the non-obese group of women.

Fig 5.3 features graphic representation of table 4.5 and 4.6 showing the effect of glucose tolerance and maternal obesity on development of macrosomia. None of the differences in proportion of macrosomia in the two subgroups in table 4.5 and table 4.6 achieved statistical significance of $p<.05$.

The graphic representation highlights the following points:

1 The proportion of macrosomic babies is significantly higher in the non-GDM obese women than in the non-GDM non-obese women.

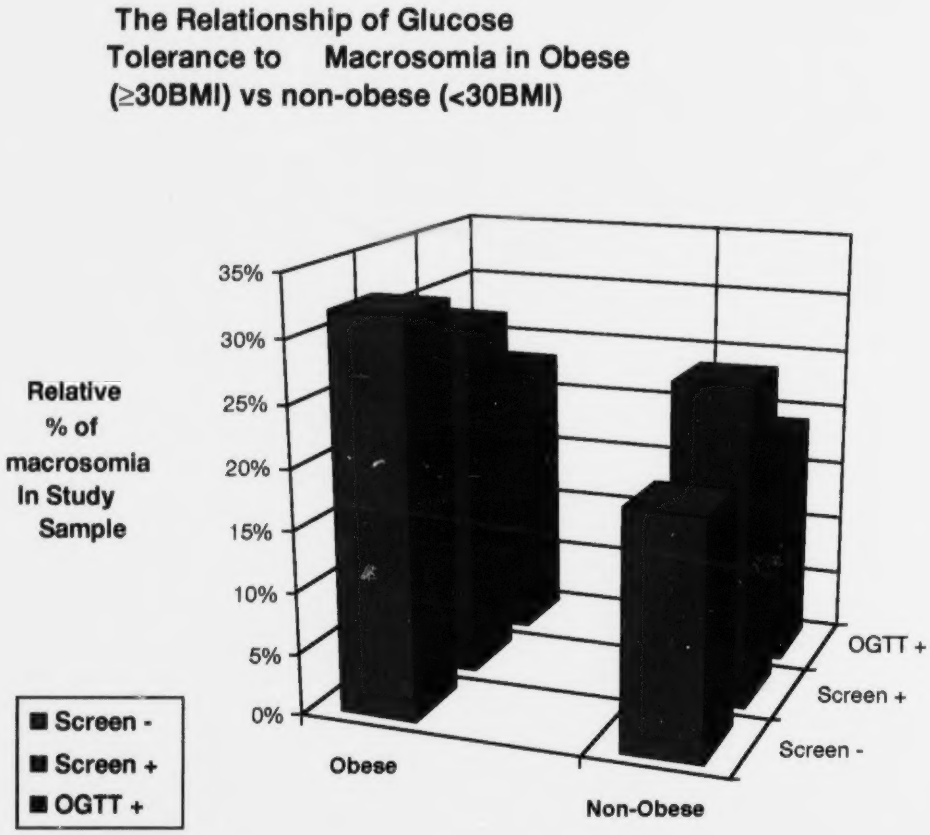
2 The proportion of macrosomic babies in the GDI-obese women is greater than in the GDI non-obese women, whereas this proportion in the GDI-obese group is less than the proportion of macrosomia in the non-GDM obese women.

3 The proportion of macrosomic babies in the GDM-obese women is greater than in the GDM non-obese women, whereas the proportion of macrosomia in the GDM-obese group is less than the proportion of macrosomia in the non-GDM obese women.

Graphic representation of table 5.5 and 5.6 showing the effect Of glucose tolerance and maternal obesity on development of macrosomia:

(p=ns as p >.05)

Fig 4.3



3. Interaction Between Maternal Obesity And Glucose Intolerance

In the multiple logistic model I and II, the GDI group was the last parameter to enter at $p<.05$ with an odds ratio of 1.7 (95%CI of .99-2.7).

As Spellacy et al.[8] in 1985 had stressed the additive nature of risk factors like GDM and obesity for developing macrosomia, we examined glucose intolerance for any synergistic effect with maternal obesity for development of fetal macrosomia. For the model testing this interaction, glucose intolerance was categorized as non-GDM, intermediate gestational diabetes (GDI) and GDM group (treated). Maternal obesity was defined as $BMI \geq 30$. Dependent variable was macrosomia.

The five groups examined by this logistic regression model with reference to the non-obese glucose tolerant pregnant subjects were:

Obese non-GDM
Obese GDI
Obese GDM
Non-obese GDM
Non-obese GDI

Interaction Terms : Odds Ratios And p-values
Response variable: Macrosomia

table 4.14

	'Birthweight≥4000g'			'LGA>90th centile'	
Variables	N	OR	p-value	OR	p-value
Obesity GDM	13	1.3	0.71	1.6	0.45
Obesity GDI	14	1.7	0.37	2.2	0.19
Obesity	85	2.0	0.006*	2.3	0.001*
Non-Obesity GDM	37	1.0	0.99	1.4	0.34
Non-Obesity GDI	99	1.5	0.09	1.8	0.03*
Non-obese Non-GDM	751	1.0(reference category)		1.0	-

N: Number of subjects; OR: odds ratio * statistically significant p-value

Categories found to be statistically significant ($p<.05$) predictors of macrosomia by this model were 'obese non-GDM' women and 'non-obese GDI' women (i.e. + GCT only), as illustrated in table 4.14. On analyzing the results of tables 4.14 and 4.15, it was clear that the average birthweight in the categories of 'obese mothers' or 'GDI with obesity' is greater by 175 grams or more than in the reference category of 'non-GDM non-obese'. By the interaction model, 'GDI non-obese' turned out statistically significant but not 'obese GDI'. It may be so because of small number of subjects in the category of obese GDI (n=14) as compared to the category of non-obese GDI (n=99).

Finally, to ascertain the clinical significance of some of the categories which were found to be statistically significant, I calculated the average baby birthweights in six groups stratified on the basis of maternal obesity and levels of glucose tolerance, thus highlighting differences in birthweights among the various groups. The direct application of table 4.15 was in finding differences in birth weights on the basis of different maternal characteristics and determining any clinically significant conclusions from the statistically significant numbers.

Table of average birthweights where N=1000 with number of macrosomics=209

Table 4.15

Maternal Groups	Average birthweight in grams	
	obesity as BMI $\geq$30	obesity as pre-preg wt $\geq$90kg
I Non-obese	**3506**	**3518**
Non-GDM	n=751	n=793
II Obese	**3774**	**3802**
Non-GDM	n=85	n=43
III Non-obese	**3581**	**3575**
GDI	n=99	n=105
IV Obese	**3684**	**3835**
GDI	n=14	n=8
V Non-obese	**3570**	**3590**
GDM	n=38	n=43
VI Obese	**3561**	**3447**
GDM	n=13	n=8

Furthermore, a subset of the total population (n=1000) was created. The purpose was to have the same rate of macrosomia in this set as in the general population of term babies (≥36 weeks). For this subset, 100 macrosomic babies were randomly selected from 209 macrosomic babies and were combined with 790 non-macrosomics, making a set of 890 babies with an 11.3% rate of macrosomia which is similar to the rate of macrosomia in the term population at RAH. Thereafter, absolute birthweights for the following categories of subjects were calculated:

Table of average birthweights, where N=890
and number of macrosomics=100

Table 4.16

Variable	n	grams	std. dev.
I.Average birthweight	890	3448g	471
Males	469	3517g	482
Females	421	3370g	445
II. Obesity (≥30 BMI)			
Non- GDM & Obese mother	71	**3655g**	442
III. Glucose Intolerance & Maternal Wt			
GDM & Obese mother	12	3517g	513
GDM & Non-Obese mother	33	3443g	457
GDI & Obese mother	13	**3614g**	595
GDI & Non-Obese mother	84	3451g	493
IV. Gestational Age			
36-40weeks	485	3339g	458
40^+-42weeks	388	**3588g**	453
>42weeks	17	3363g	369
V. Smoke			
Smoking	270	**3322g**	438
Non-Smoking	620	3502g	475
VI. North American Aboriginal	58	**3578g**	537

Birthweights that were different by more than 100g from the population average have been highlighted. In the highlighted category II (obesity) and III (GDI with obesity), the difference in birthweights from the population average was close to 200 grams and was directly attributable to maternal obesity irrespective of the glucose tolerance status. No difference in birthweight could be found between 'GDI non-obese' or 'GDM (treated)-non obese' and the population average. Again, in the category of GDM with obesity, the average birth weight was 69g more than the population average.

In category IV, the heaviest babies were between 40-42 weeks gestation.

Smoking has a negative correlation with birthweight, and with incidence of macrosomia. Birthweight among women who smoked during the index pregnancy was 100 grams less than the population average and newborns of non-smokers were heavier by 50 grams than the population average.

The newborns of North American Aboriginal mothers were 130 grams heavier than the population average.

CHAPTER 5

RESULTS II: PREDICTORS OF DISPROPORTIONATE FAT DISTRIBUTION

PREDICTORS OF DISPROPORTIONATE FAT DISTRIBUTION

This chapter deals with anlaysis of objective II. Univariate as well as multivariate analyses were applied for finding the relative importance of the predictors of disproportionate growth in newborns. Measures of disproportionate growth examined were:

1. Ponderal Index (birthweight x 100/height^3) (PI)
2. Mid-arm circumference:Head circumference (MAC:HC)
3. Abdominal circumference:Head circumference (AC:HC)

A. COMPARISON OF THE MEAN VALUES

(i) Ponderal Index (P.I.)

T-test was applied for comparison of mean values of ponderal index measured on continuous scale. Variables to be tested were subgrouped as neonatal factors and maternal factors.

Table of mean values:PI

Table 5.1

	VARIABLES	N	MEAN OF P.I.	p-Value
	Neonatal			
A.	LGA	821	2.92	0.0001*
	Non-LGA	179	2.71	
B.	Macrosomia	790	2.89	0.0001*
	Non-Macrosomia	210	2.70	
C	Male Baby	539	2.73	0.87
	Female Baby	462	2.76	
	Maternal			
D.	Obese (wt≥90kg)	942	2.75	0.94
	Non-obese	59	2.74	
E.	BMI<30kg/m^2	889	2.75	0.46
	BMI30-34kg/m^2	74	2.75	
	BMI≥35kg/m^2	38	2.79	
F.	Non-GDM	838	2.74	0.11
	GDI	113	2.75	
	GDM	50	2.81	
G.	Gestational Age			
	< 40weeks	485	2.7	0.76
	40-42weeks	388	2.7	
	>42weeks	17	2.6	

*p-value statistically significant. N-number of subjects

The average standard deviation of ponderal index for the entire population was 0.25. Ponderal index was statistically significantly different between the macrosomic and the non-macrosomic newborns but the difference was small. Ponderal index was not statistically different due to factors like baby's gender, maternal obesity, glucose tolerance status or gestational age.

(ii) Mean Values of MAC:HC and AC:HC

Table of mean values: MAC:HC & AC:HC

Table 5.2

		MAC:HC	AC:HC
	Neonatal		
A.	Macrosomia	0.33*	0.94*
	Non-Macrosomia	0.31*	0.91*
B.	Male Baby	0.31	0.90
	Female Baby	0.31	0.92*
	Maternal		
C	Gestational Age		
	< 40weeks	0.31	0.91
	40-42weeks	0.31	0.91
	>42weeks	0.31	0.89
D.	Non-GDM	0.31	0.91
	Intermediate	0.31	0.91
	GDM	0.32	0.93

*p-value statistically significant

The average standard deviation of MAC:HC and AC:HC was 0.02 and 0.05 respectively. The mean values of MAC:HC and AC:HC were statistically significantly (p<.05) different for the two categories in group A only. The p-values for all the other groups were >.05 and so not significantly different between the categories.

B. CORRELATIONS

Correlations between the different measures of disproportionate growth and neonatal/maternal factors were examined by Pearson correlation coefficient, r.

Table of correlations

Table 5.3

VARIABLES			P.I.	MAC:HC	AC:HC
Neonatal					
1.	Birth weight	r	0.37	0.53	0.34
		p	0.0001*	0.00*	0.0001*
2.	Female gender	r	0.06	0.02	0.09
		p	0.04*	0.33	0.0002*
Maternal					
3.	Pre-preg wt	r	0.02	0.07	0.06
		p	0.55	0.01*	0.05*
4.	GDM	r	0.05	0.08	0.09
		p	0.04*	0.01*	0.003*
5.	Maternal Height	r	-0.05	0.03	0.07
		p	0.07	0.20	0.03*
6.	Weight gain	r	0.06	0.143	0.12
		p	0.22	0.00*	0.006*
7.	Gestational Age	r	0.05	0.10	0.008
		p	0.08	0.001*	0.4
8.	Parity	r	0.05	0.06	0.05
		p	0.06	0.01*	0.05*
9.	North American Aboriginal	r	0.04	0.08	0.12
		p	0.15	0.006*	0.00*
10.	Maternal Age	r	0.03	0.07	0.004
		p	0.15	0.02*	0.5

r: Pearson's correlation coefficient; p: *statistically significant

Newborn's birthweight was found to have statistically significant correlation with the all the three measures of disproportionate growth. Some of the other examined variables like female sex, pre-pregnancy weight, weight gain, maternal height, North American aboriginal status etc.. did achieve statistically significant correlations but the correlation coefficient was very small and those small 'r' values do not explain much variability of clinical importance in the outcome. Presumably, statistically significant p-values for variables like pre-preg wt, maternal height, weight gain and North American Aboriginal etc.. could be due to their effect on birthweight itself. All these variables have further been examined by the multivariate model.

There is not adequate published information on predictors of disproportionate growth, though there is speculation on the role of genetic factors or metabolic factors of glucose intolerance, on the outcome of disproportionate fat distribution. All the variables mentioned above were further examined by multivariate methods to delineate any independent effects without confounding or co-variance, of these variables on the outcome of disproportionate fat distribution.

C. LEAST SQUARES REGRESSION ANALYSIS

Univariate statistical methods (table 5.1 5.2 5.3) were used as a first step to examine the association of different variables with the outcome. Initial analysis and assumptions based on the theoretical framework led to the model for testing by step-wise least squares regression technique.

Measures of disproportionate growth examined as dependent variables (on continuous scale) by the model were:

1. Ponderal Index (birthweight x 100/height^3)
2. Mid-arm circumference:Head circumference
3. Abdominal circumference:Head circumference

Independent variables examined by the model were:

Neonatal:

a) Birth weight on continuous scale

b) Gender
male=0 female=1

Maternal:

a) Pre-pregnancy weight

On continuous scale

c) Parity

Para 1=1

Para≥ 2=2

else, Nulliparous=0

d) Maternal Height

On a continuous scale

e) Gestational Age

On a continuous scale: 36 37 38 ......>42 weeks

f) Gestational diabetes mellitus

(treated) - GDM

g) Impaired Glucose Tolerance

- GDI

h) North American Aboriginal women

i) Maternal Age- On a continuous scale

Each measure of disproportionate growth was examined independently by the stepwise procedure producing results shown in tables 5.4 a b c.

a. Response variable: Ponderal Index

Predictors of Increasing Ponderal Index (n=890)

table 5.4a

	B	SE	p value	R^2(cumulative)
a. Birthweight g	.00019	(.00..)	0.0001*	0.13
b. Maternal Height	-.47	(.11)	0.0001*	0.15
c. Female Sex	.6	(.015)	0.0001*	0.17

B: parameter estimate (coefficient); SE: standard error of coefficient;
R^2: model R-squared; * statistically significant

The variance explained by birthweight was 13%. Though other independent variables like gender and maternal height entered the model at p<.05, the collective variance explained by them was 4% only. On examining the mean values table (5.1), it was clear that the statistical significance (p<.05) achieved by gender was purely due to a large sample size and would have no clinical significance. In addition, the finding of maternal height being negatively correlated with increasing PI does not have much clinical significance.

b. Response variable: MAC:HC

Predictors of Increasing MAC:HC Ratio (n=890)

Table 5.4b

	B	SE	p value	R^2 (cumulative)
a. Birthweight g	.00002	(.00..)	0.000*	0.28
b. Female Sex	.005	(.0014)	0.0002*	0.29
c. Maternal Ht	-.03	(.01)	0.002*	0.30

B: parameter estimate (coefficient); SE: standard error of coefficient; R^2: model R-squared; * statistically significant

The variance explained by birthweight was 28%. Though other independent variables, such as gender and maternal height entered the model at p<.05, the variance explained by either one of them was only 1%.

c. Response variable: AC:HC ratio

Predictors of Increasing AC:HC Ratio (n=890)

Table 5.4c

	B	SE	p value	R^2 (cumulative)
a. Birthweight	.00003	(.00..)	.0001*	0.12
b. Female Sex	.024	(.003)	.0001*	0.18
c. North American Aboriginal woman	.018	(.006)	.002*	0.19

B: parameter estimate (coefficient); SE: standard error of coefficient; R^2: model R-squared; * statistically significant

The variance in AC:HC was 12% explainable due to the newborn's birthweight. Female gender entered the model next with an explainable variance of 6%. Ethnicity had negligible independent effect (variance 1%) on AC:HC.

D. ABSOLUTE VALUES AND GRAPHS

Given below in Table 5.5 are the absolute values and standard deviation of PI, MAC:HC and AC:HC in the following categories of variables

a. Macrosomia vs. Non-macrosomia
b. Levels of glucose tolerance: non-GDM, GDI, GDM
c. Gestational age
d. Male vs. female

Bar graphs (fig 5.1, 5.2, 5.3, 5.4) are the graphic representation of absolute values shown in the table below.

Average Values and Std Dev Of PI, MAC:HC and AC:HC
(n=890)

Table 5.5

Variables		PI	MAC:HC	AC:HC
a.	Birthweight			
	Macrosomia	2.92±.24	.33±.02	.94±.04
	Non-macrosomia	2.71±.24	.31±.02	.91±.05
b.	Glucose tolerance			
	Non-GDM	2.73±.25	.31±.02	.91±.05
	GDI	2.74±.23	.31±.03	.92±.04
	GDM	2.80±.31	.32±.02	.93±.05
c.	Gest Age			
	36-40 weeks	2.75±.24	.31±.02	.92±.05
	40-42 weeks	2.72 ±.25	.31±.02	.92±.05
	>42 weeks	2.60±.20	.31±.03	.90±.04
d.	Gender			
	Male	2.72±.24	.31±.02	.90±.05
	Female	2.75±.25	.31±.03	.92±.05

fig 5.1

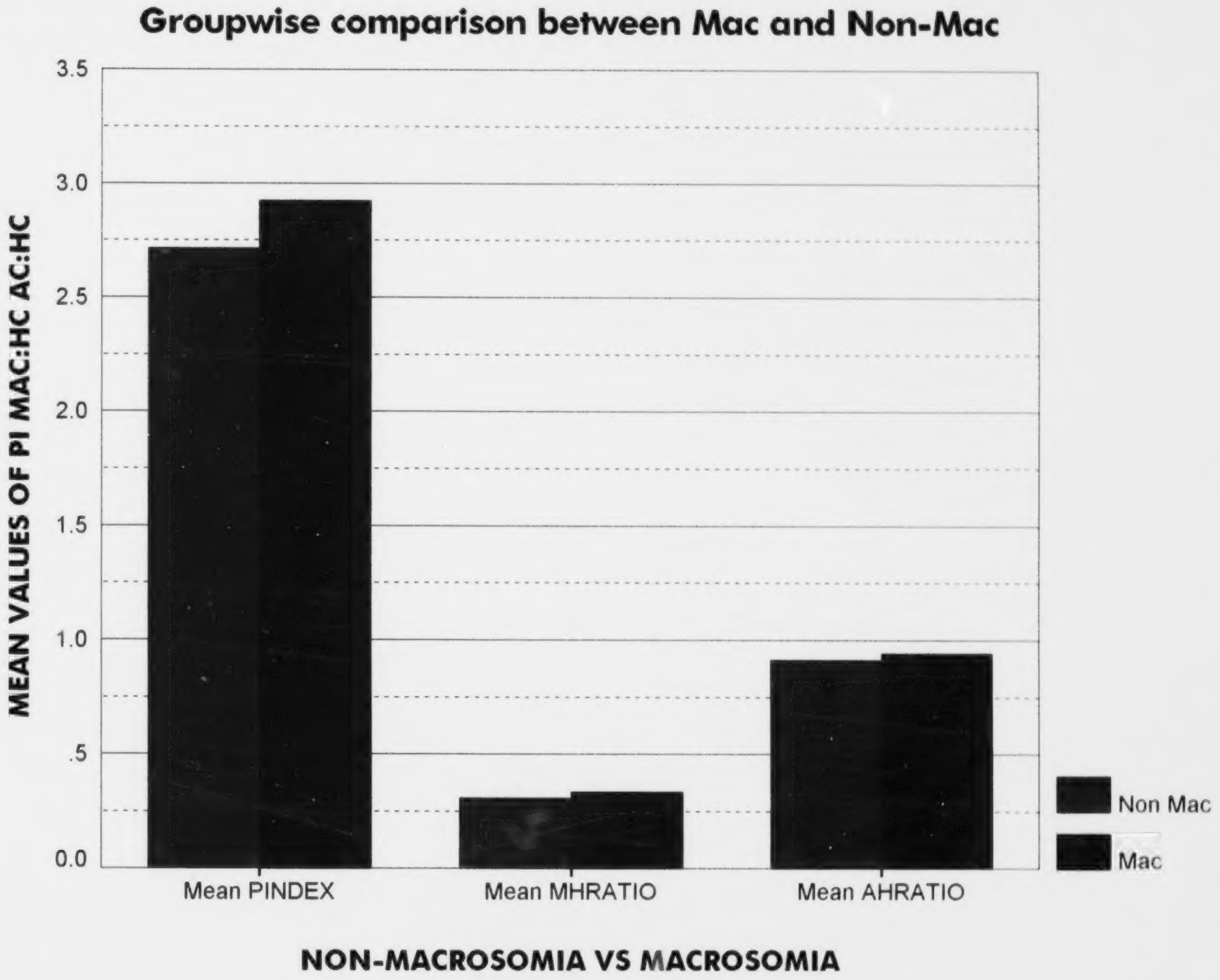

Groupwise comparison between Mac and Non-Mac
MEAN VALUES OF PI MAC:HC AC:HC
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
Mean PINDEX
Mean MHRATIO
Mean AHRATIO
Non Mac
Mac
NON-MACROSOMIA VS MACROSOMIA

fig 5.2

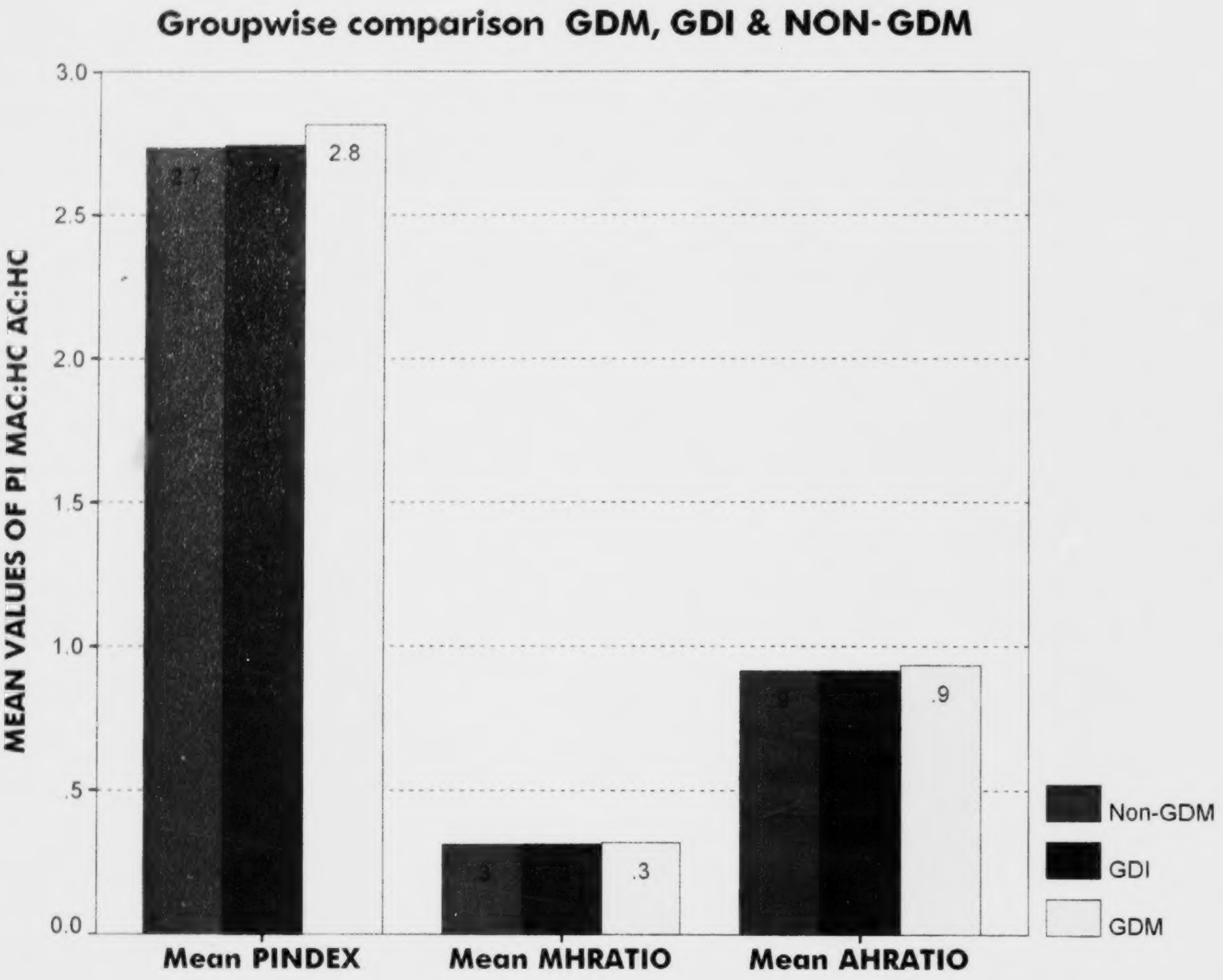
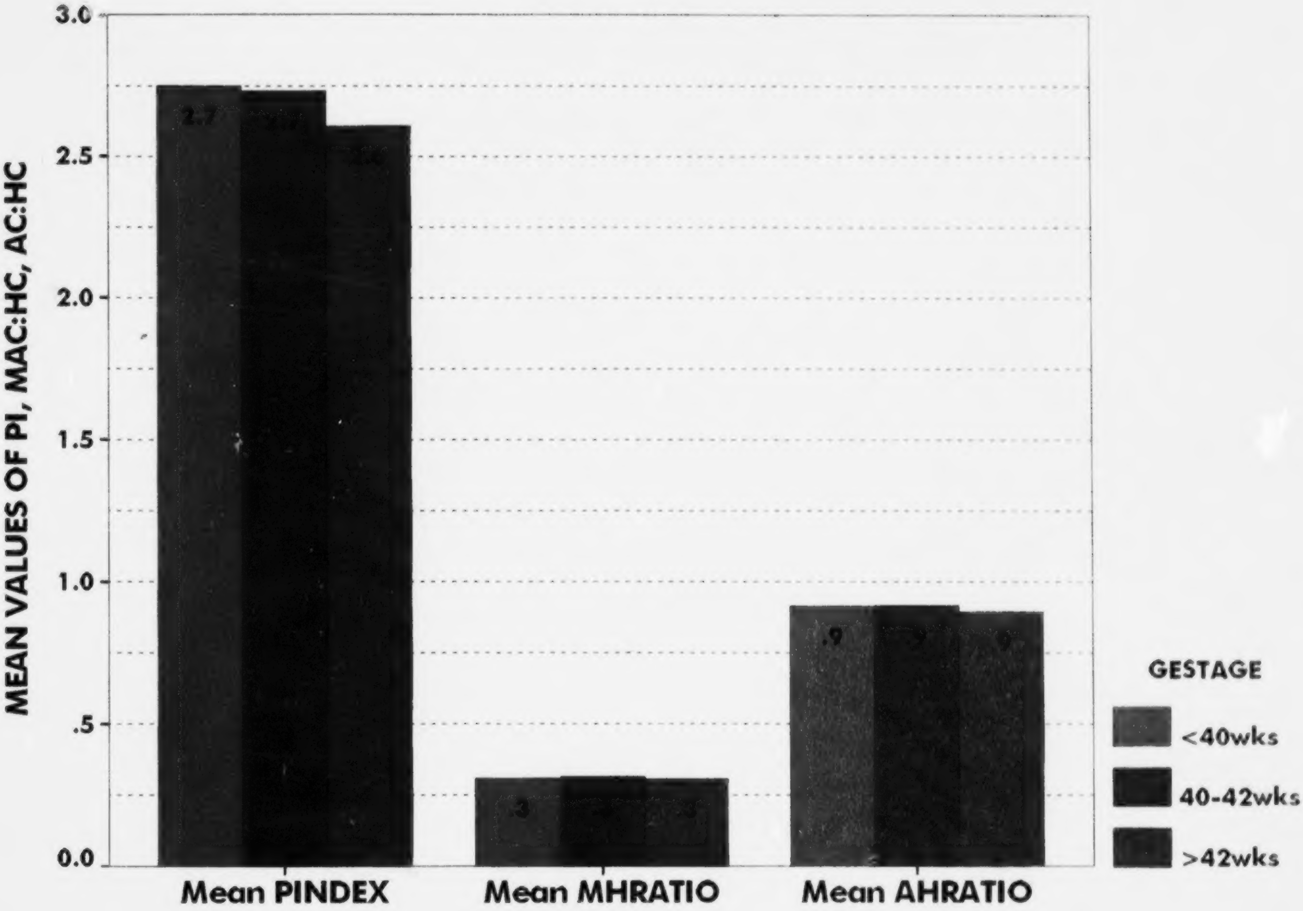
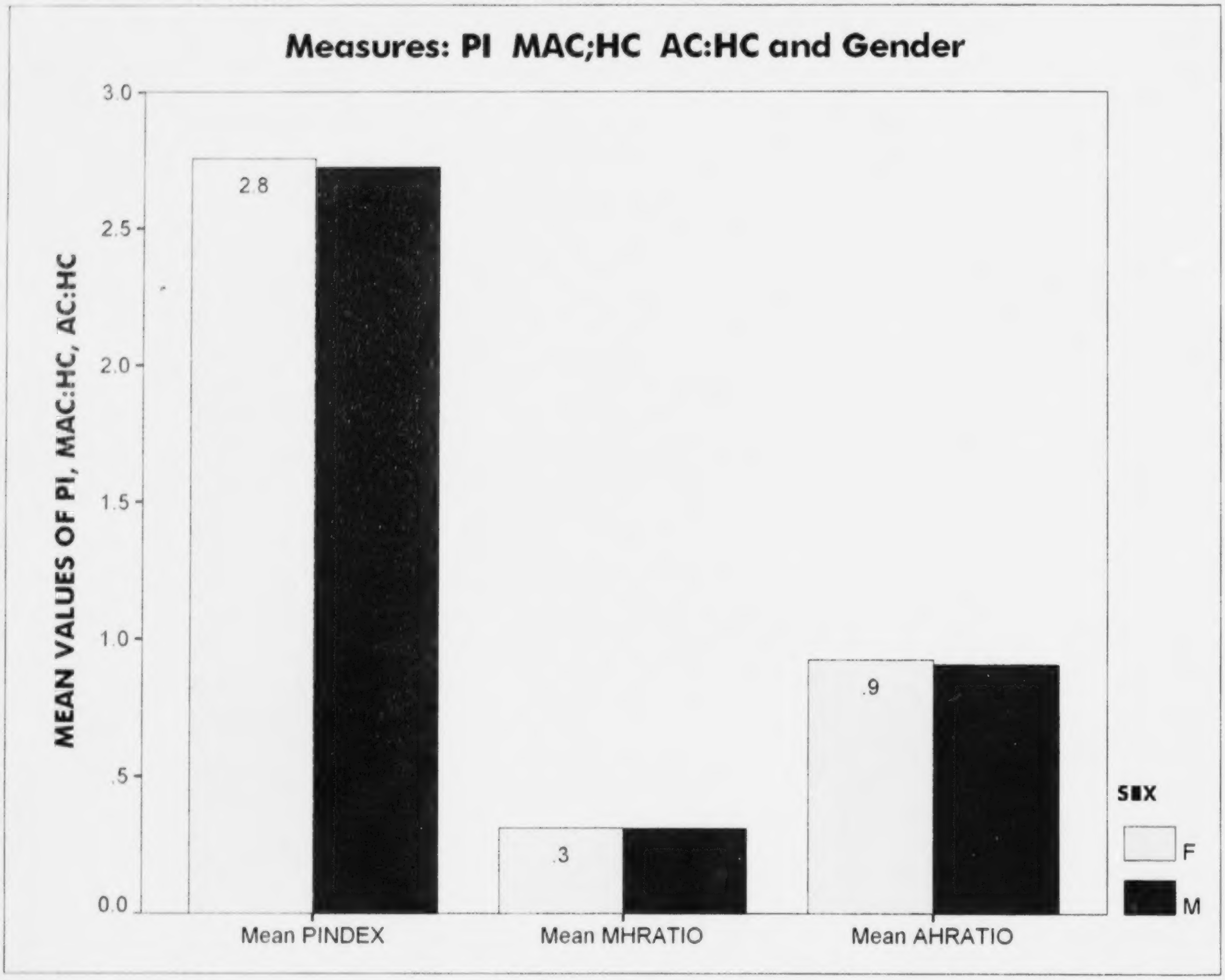

Groupwise comparison GDM, GDI & NON-GDM
MEAN VALUES OF PI MAC:HC AC:HC
3.0
2.5
2.0
1.5
1.0
.5
0.0
2.7
2.7
2.8
.3
.3
.9
.9
Mean PINDEX
Mean MHRATIO
Mean AHRATIO
Non-GDM
GDI
GDM

fig 5.3



Measures Of Disproportionate Growth by Gestage

fig 5.4


Measures: PI MAC;HC AC:HC and Gender
MEAN VALUES OF PI, MAC:HC, AC:HC
3.0
2.5
2.0
1.5
1.0
.5
0.0
2.8
.3
.9
Mean PINDEX
Mean MHRATIO
Mean AHRATIO
SEX
F
M

E. MULTIVARIATE ANALYSIS OF THE MEASURES AT >90TH PERCENTILE

In the study of risk factors for shoulder dystocia, Acker et al.[43] found that diabetic gravidas experienced shoulder dystocia five times more often than non diabetic women. Acker et al. considered a gravida to be diabetic if she either required insulin before or during the current pregnancy or had an abnormal OGTT during the current pregnancy. Modanlou et al.[19] noted that the neonates who experienced shoulder dystocia had greater shoulder-to-head ratios and chest-to-head ratios than the control population. Therefore, because of the possible role of fat distribution in birth trauma and shoulder dystocia, it is important to be able to define possible determinants of disproportionality, other than the birth weight itself.

I examined the subjects at >90th percentile of PI or MAC:HC or AC:HC by further multivariate analysis. The purpose of this last exercise was to thoroughly screen determinants if any, other than the birthweight, of disproportionate fat distribution in newborns. Independent variables examined by this model were: gestational age, newborn's birthweight, gender, maternal age, maternal BMI, weight gain, ethnicity, GDI and GDM.
Stepwise least squares regression was applied to the following dependent variables using three separate models:

a. newborns at >90th percentile of PI i.e. >3.05
n=113
No variables entered the model at $p<.05$

b. newborns at >90th percentile of MAC:HC i.e. >0.34
n=119
Only birthweight entered the model at $p<.05$ with explainable variance (R^2) of 3%.

c. newborns at >90th percentile of AC:HC
n=118
Only female sex entered the model at $p<.05$ with explainable variance (R^2) of 5%.

Apparently, there were no determinants of >90th percentile PI in the model tested. Generally, newborns with an increasing birthweight have an increasing height as well, that moderates values of the ponderal index for the big babies. Therefore, increasing absolute birthweight ceases to be a determinant of increasing PI.

There were no additional determinants of increasing MAC:HC ratio and entry of the variable, birthweight at $p<.05$ with R^2 of only 0.03 is of doubtful clinical value.

Female gender entered the model for increasing AC:HC ratio. The percentile table 7.3 in chapter 7 also reveals that females have slightly higher values of AC:HC ratio with increasing birthweight but again R^2 of only 0.05 is of doubtful clinical value.

CHAPTER 6

RESULTS III: PLASMA GLUCOSE VALUES & BIRTHWEIGHT

This section deals with analysis of objective III. We sought to investigate whether the extent of glucose abnormality as reflected by the mean of plasma glucose values, correlates with fetal macrosomia.

We examined the relationship between:

1) 50 g glucose screen test values in screen-positive women, and fetal macrosomia (defined as ≥4000g as well as >90th centile)

2) 100 g OGTT values of intermediate and gestational diabetic group of subjects, and fetal macrosomia

3) GCT, OGTT values, the average of fasting and the average of post-meal blood glucose values among treated gestational diabetics, and fetal macrosomia, by the univariate as well as the multivariate model.

The statistical analysis was carried out with SAS on the mainframe computer. Data were evaluated using t-test, Pearson's correlation coefficient and stepwise multiple regression analysis. Dependent variable was binomial with birthweight categorized into macrosomia and non-macrosomia.

Distribution of the subjects studied for plasma glucose values: n =1000

Table 6.1

Characteristics	Number
Non-GDM	949
(GCT-)	836
Intermediate (GCT+ & OGTT-)	113
GDM	50
Diet Therapy	37
Insulin+diet Therapy	13
Prepreg Wt ≥ 90kg	59
BMI ≥30	112
Data available on:	
GCT+ & OGTT -	112; (missing OGTT values in 1 subject)
GCT+ & OGTT+	47; (missing OGTT values in 3 subjects, though they were treated as GDM)
Fasting & Post-Prandial values on glucometers	46 (record misplaced by one subject)

46% subjects in the insulin therapy group were obese (≥30BMI), whereas only 16% subjects were obese in the diet therapy group. The birthweight and maternal characteristics in these two groups were as below:

	'diet' (n=37)	vs	'insulin+diet' (n=13)
birthweight	3515g±540	vs.	3706g±437
average maternal weight	64.43kg±15.3	vs.	80.4kg±28.8
average BMI	24.1kg/m^2±5.1	vs.	29.7kg/m^2±8.3

A. COMPARISON BETWEEN MACROSOMICS AND NON-MACROSOMICS

Differences In Plasma Glucose Values

The babies were grouped as macrosomic and non-macrosomic by both the definitions of macrosomia i.e. by absolute birthweight and by large for gestational age (>90th percentile for gestational age by gender).

Analysis was done using t-test on the following plasma glucose levels measured on continuous scale:

1. GCT value
2. OGTT value: fasting, 1-hour, 2-hour, 3-hour
3. Treated GDM: readings of the average of fasting and of the average of post-prandial (PP), recorded on home glucometers.

Intermediate Group

The plasma glucose values of intermediate group (GDI) of subjects (n=112) were compared between the macrosomics and the non-macrosomics:

Table Of Comparison
Intermediate (GDI) Group
(n=112)

Table 6.2

	LGA			Macrosomia		
Mean Glucose Value(mmol/l)	non-LGA (n=84)	LGA (n=28)	p	non-Macro (n=82)	Macro (n-30)	p
GCT	8.6	8.7	0.78	8.7	8.6	0.59
OGTT(fasting)	4.5	4.5	0.60	4.5	4.6	0.37
OGTT (1-hour)	8.2	8.5	0.40	8.2	8.4	0.61
OGTT (2-hour)	7.4	7.3	0.75	7.4	7.2	0.29
OGTT (3-hour)	6.2	5.9	0.33	6.2	6.0	0.55

none of the p-values are statistically significant

Table 6.2 shows that the plasma glucose values of GCT and OGTT (F, 1hr, 2hr, 3hr) were not significantly different between the macrosomic and the non-macrosomic category of newborns in the intermediate group.

GDM Group

The plasma glucose values among GDM group of subjects (n=47) were compared between the macrosomics and the non-macrosomics:

Table Of Comparison
GDM Group (treated)
(n=47)

Table 6.3

	LGA			Macrosomia		
	non-LGA	LGA	p	non-Macro	Macro	p
GCT	9.1	9.7	0.12	9.1	9.6	0.29
OGTT(fasting)	4.9	5.1	0.45	4.9	5.1	0.45
OGTT (1-hour)	11.0	11.2	0.74	11.0	11.2	0.74
OGTT (2-hour)	9.6	8.5	0.12	9.6	8.5	0.12
OGTT (3-hour)	7.7	6.2	0.07	7.7	6.3	0.07
Treated GDM						
Average of Fasting	4.7	5.3	0.006*	4.8	5.3	0.01*
Average of PP	5.5	6.0	0.01*	5.5	6.0	0.04*

*-p-value statistically significant

The plasma glucose values of GCT and OGTT were not significantly different between the macrosomic and the non-macrosomic category of newborns in the GDM subjects .

Out of the total 50 subjects diagnosed as GDM, 37 were treated by diet only and 13 were treated by diet and insulin. Data on values of average fasting and average PP were available on 46 subjects only. The values of average fasting and average PP as recorded by patients on home glucometers were statistically significantly different between the macrosomics and the non-macrosomics. The average fasting glucose was greater by 0.60 and the average post-prandial was greater by 0.50 in macrosomics as compared to non-macrosomics.

B. CORRELATION BETWEEN PLASMA GLUCOSE VALUES AND BIRTHWEIGHT

Analysis was done using the Pearson's correlation coefficient.

Birthweight was analyzed as variable on continuous scale.

Impaired glucose tolerance was subgrouped as GDI (intermediate group) and GDM (treated).

Intermediate Group

Table of correlation
Intermediate (GDI) Group (n=112)

Table 6.4

Plasma glucose value of	r	p
GCT	-0.03	0.79
OGTT(fasting)	0.10	0.27
OGTT(1-hour)	0.09	0.36
OGTT(2-hour)	-0.07	0.43
OGTT(3-hour)	-0.15	0.12

r: correlation coefficient between birthweight and plasma glucose values
p: statistically not significant at $p>.05$

In the intermediate group, there were no statistically significant correlations between the values of 50g glucose challenge test or the individual values of 100g OGTT (fasting, 1hr, 2hr, 3hr) and the newborn's birth weight.

GDM Group

Table Of Correlation
GDM Group (treated) (n=46)

Table 6.5

Plasma glucose value	r	p
GCT	0.34	0.01*
OGTT(fasting)	0.17	0.26
OGTT(1-hour)	0.15	0.30
OGTT(2-hour)	-0.17	0.26
OGTT(3-hour)	-0.27	0.07
GDM treated		
Average Of Fasting	0.46	0.001*
Average Of PP	0.38	0.01*

r: correlation coefficient between birthweight and plasma glucose values *p-value statistically significant

On analyzing correlation between the plasma glucose values of GCT, OGTT (fasting, 1hour, 2hour and 3hour); the average of fasting and the average of postprandial readings in the gestational diabetic women, and the newborn's birth weight; we find that there is a statistically significant positive correlation between the newborn's birthweight and (a) the values of the 50g GCT (r=0.34), (b) the values of the average fasting plasma glucose (r=0.46) and (c) the values of the average post-prandial plasma glucose (r=0.38), as shown in the table above.

C. MULTIPLE LOGISTIC REGRESSION

Further using the multiple logistic regression model, association of different plasma glucose levels with the outcome of macrosomia was examined. Macrosomia (by both the definitions) was examined as a dependent dichotomous variable coded as below:

0=non-macrosomia
1=macrosomia

Models of the intermediate and the GDM groups were examined separately with the following plasma glucose levels as independent continuous variables:

GCT value
OGTT value: fasting, 1-hour, 2-hour, 3-hour
Average of fasting (F)
Average of post-prandial (PP)

Intermediate Group:

Response variable: Macrosomia
Number of observations: 112

Stepwise regression showed that none of the plasma glucose levels (GCT value, OGTT values: fasting, 1-hour, 2-hour, 3-hour) were statistically significantly (p<.05) associated with the outcome of macrosomia.

GDM (treated) Group:

Response variable: Macrosomia
Number of observations: 46

Among GDM subjects, the only parameter to enter the model at $p < .05$ was 3-hr OGTT value, and it was found to be negatively correlated with the outcome of macrosomia (see table 6.6).

Results of multiple logistic regression (GDM group)

Table 6.6

	ß	p-value
3 hr OGTT	-.71	.02*

The variables that did not meet the $p<.05$ significance level of entry are as in table 6.7.

Variables not in the model

Table 6.7

Variable	Score Chi-Square	p
Average Fasting	3.8	.06
GCT	0.77	.37
OGTT		
Fasting	0.23	.63
1 hr	1.0	.31
2 hr	1.8	.18
Average PP	0.54	.46

CHAPTER 7

RESULTS IV
NOMOGRAMS

The results section-II revealed that newborn's birthweight has an independent, positive correlation with all the three measures of disproportionate fat distribution, namely: PI, MAC:HC and AC:HC (R^2 being 0.13, 0.28 and 0.12 respectively). Gestational age in term babies ($\geq$36weeks gestation) does not significantly alter any of the measures of disproportionate growth. Gender also does not alter the mean values of these measures appreciably.

Nomograms based on the 10th, 50th and 90th percentile values of PI, MAC:HC and AC:HC within different categories of birth weight for term, normal, singleton newborns were compiled in tables 7.1, 7.2 and 7.3. Values for male newborns and female newborns are given in separate columns in order to substantiate the fact that gender does not alter these measures significantly.

Percentiles of PI, MAC:HC and AC:HC for singleton, live, normal, healthy, term newborns

Percentile of Ponderal Index by Sex

Table 7.1

	Males				Females			
Birthweight	Percentile: PI				Percentile: PI			
grams	N	10	50	90	N	10	50	90
2000-2499g	6	1.8	2.4	2.7	3	2.2	3.0	3.1
2500-2999g	51	2.3	2.6	3.0	90	2.4	2.6	3.0
3000-3499g	178	2.4	2.6	2.9	174	2.5	2.7	3.0
3500-3999g	167	2.5	2.8	3.1	121	2.5	2.8	3.1
4000-4499g	48	2.6	2.9	3.1	26	2.6	3.0	3.1
>4500g	19	2.6	3.0	3.4	7	2.8	2.9	3.5

Average Standard deviation for PI = ±0.24

Percentile of MAC:HC by Sex

Table 7.2

	Males				Females			
Birthweight	Percentile: MAC:HC				Percentile: MAC:HC			
grams	N	10	50	90	N	10	50	90
2000-2499g	6	.24	.30	.31	3	.25	.28	.30
2500-2999g	51	.27	.29	.32	90	.27	.29	.32
3000-3499g	178	.28	.30	.33	174	.28	.30	.34
3500-3999g	167	.29	.32	.35	121	.29	.32	.35
4000-4499g	48	.30	.33	.36	26	.30	.34	.37
>4500g	19	.32	.34	.38	7	.32	.35	.36

Average Standard deviation for MAC:HC= ±0.02

Percentile of AC:HC by Sex

Table 7.3

	Males				Females			
Birthweight	Percentile: AC:HC				Percentile: AC:HC			
grams	N	10	50	90	N	10	50	90
2000-2499g	6	.79	.82	.88	3	.85	.86	.88
2500-2999g	50	.85	.90	.94	87	.84	.90	.96
3000-3499g	173	.84	.89	.94	168	.87	.92	.98
3500-3999g	164	.86	.91	.97	119	.88	.94	.99
4000-4499g	47	.87	.92	.97	26	.89	.95	1.0
>4500g	19	.91	.96	.99	7	.91	.97	1.0

Average Standard deviation for AC:HC= ±0.05

Tables of percentiles have been categorized by sex, only to highlight the fact that female babies in spite of being lighter and of smaller frame, have nearly the same values of PI, MAC:HC and AC:HC as their male counterparts.

Smaller values of PI for males in the 2000-2499g category can be explained by their greater height as compared to females in the same weight category. With increasing weight, AC:HC ratio has slightly higher values for female babies as compared to their male counterparts; presumably because of greater fat deposition in the female newborns than in the male newborns.

Because the proportion of babies in weight group 2000-2499g was small, the figures reported for the 90th centile (table 7.1-7.3) are subject to statistical instability.

CHAPTER 8

DISCUSSION & CONCLUSIONS

A. Predictors of macrosomia

The pathophysiology of macrosomia represents a complex interrelation and interaction of modifiable and non-modifiable, genetic and metabolic factors. It is not possible to modify most of these risk factors with an aim to prevent macrosomia. However, all the risk factors are useful in predicting or identifying the large for gestational age baby.

We used both the large-for-gestational age and the absolute birthweight criteria as markers of accelerated growth. Using LGA criteria precluded the need to make adjustments for gestational age and gender. It is important to mention though that the results of the univariate and the multivariate analyses were very similar in spite of using these two different criteria.

Our analysis confirms previous reports of the effects of a variety of maternal and fetal variables on fetal growth[8 11]. Spellacy et al.[8] in 1985, examined the maternal characteristics and infant complications in macrosomic (>4500 g) vs. non-macrosomic newborns. He found three significant maternal risk factors for fetal macrosomia, namely post-maturity (longer than 42 weeks gestation), obesity (greater than 90 kg weight at delivery) and diabetes (gestational and insulin-dependent types). Although this well conducted, retrospective study utilized a large database comparing 574 macrosomic infants to a control group of 18,739 non-macrosomic infants, the analyses did not examine in a multivariate fashion the independent or combined effects of the various predictors of macrosomia. In addition their study did not examine various associated maternal characteristics such as parity, ethnicity, weight gain or maternal height and age. The Spellacy study implied an additive nature of these factors. When we tested the additive nature of maternal pre-pregnancy weight and levels of glucose intolerance by using interaction terms between these two variables i.e. maternal pre-pregnancy weight x levels of glucose intolerance in a multiple logistic regression model, we did not find any synergisitc effect between maternal obesity and glucose intolerance on the outcome of macrosomia.

In a population-based study of maternal and perinatal outcome in patients with gestational diabetes, Jacobson and Cousins[11] compared 97 cases of

GDM with 2107 non diabetic control patients. Women with GDM were older, had a higher pre-pregnancy weight, had greater mean gravidity and their pregnancy weight gain was less than that of the controls. Stepped multiple regression analysis of GDM subjects (n=97) showed that maternal weight at delivery was the only significant predictor of birth weight percentile in patients with gestational diabetes mellitus. They also found that acceptable glucose control did not normalize birth weight percentiles in patients with GDM. Neonatal outcome was calculated in terms of birthweight centile (centiles developed from tables derived from data measured in neonates born at sea-level) or percentages. Statistically significant differences in percentiles of birthweight and height between groups may also be analyzed in terms of differences in absolute birthweight of newborns. In that study, stepped multiple regression was applied to only 97 subjects with GDM in an attempt to test several i.e. >15 variables. Minimum sample size to detect any statistically significant results in this multivariate model should be 150.

Johnson et al.[56] from Iowa in their well-conceived study of 'maternal obesity and pregnancy' found a significantly increased risk in the obese patient for gestational diabetes, hypertension, therapeutic induction, prolonged second stage of labor, shoulder dystocia, macrosomia and post-datism. The mean birthweight of newborns of obese patients (defined as maternal weight >250 lb at some time during pregnancy) was found to be 3,685 g and that of control patients (matched on age and parity, and weighing <200 lb during pregnancy) was 3250 g. That study was flawed in several ways. Retrospective data collection from computerized hospital discharge summaries spanned a period from 1961 till 1980, during which tremendous advances were achieved in obstetrics and neonatology thereby introducing discrepancy in the base-line population statistics. There was also a lack of standard definition for maternal obesity and a crude criteria of 'standard height adjusted weight measure' was applied because the recording of maternal height in discharge summaries was incomplete.

We sought to obviate these shortcomings in the other studies by collecting an adequate sample size, keeping power close to 90%, applying multivariate analysis to control for the effects of confounding factors, testing interaction terms, using criteria of absolute weight as well as large-for-gestational-age for newborns and pre-pregnancy weight and BMI for mothers. Patients meeting inclusion criteria were recruited at the time of hospitalization for delivery, thus enhancing collection of complete and unbiased records. Suspicion of a LGA fetus, especially in women who required insulin during pregnancy leads to obstetrical interventions at times, in the form of induction of early labour or pre-term elective cesarean section. We feared that these obstetrical interventions could result in a false negative rate of macrosomia in our study population. However, on applying LGA criteria during analysis, the nature and the order of entry of variables into the model remained almost identical to the absolute weight criteria model.

On analyzing by the multiple logistic regression model, 'previous history of macrosomia' entered first and was found to increase the risk of macrosomia defined by the birthweight criteria, by 7.3 times and that of macrosomia defined by the LGA criteria, by 9 times. By including the previous history of macrosomia into the model, the sample size gets reduced to 579, as only para≥1 subjects can be included in that model. This results in loss of power and loss of available information on the other variables. Excluding previous history of macrosomia from the model, the order of entry of variables into the stepwise regression model was maternal pre-pregnancy weight, weight gain, history of smoking (negative correlation), multiparity, male sex, ≥40 weeks gestational age, ethnicity (North American Aboriginal), maternal birthweight>4000g, maternal height, maternal age ≤17 years and GDI i.e. intermediate group. GDM did not enter this model at $p<.05$.

Below I have given an account of predictors in terms of their applicability in clinical practice:

I Non-modifiable
II Modifiable

I NON-MODIFIABLE PREDICTORS

Predictors in this category find utility in predicting macrosomia at the time of delivery.

a. Previous history of macrosomia: A woman having produced a macrosomic baby in the past is at more than 7 times the risk of delivering a macrosomic baby in the present pregnancy. The risk of macrosomia is directly proportional to the number of macrosomic babies in the past.

b. Maternal height, maternal birthweight and paternal BMI: Every 7cm increase in height above the average height of 164 cm, increases the risk of macrosomia by 30%. Paternal BMI was found to be 26.3 in fathers of macrosomic babies as compared to 25.3 in those of non-macrosomic babies. This association of birthweight with paternal BMI has to be explored further. Progeny of constitutionally taller and heavier parents tends to be taller and heavier[44 81]. The effect due to height is independent of the effect due to maternal weight and other covariates. Maternal birthweight >4000g increased the risk of macrosomia in her progeny by two fold and this effect is independent of the effect due to parental weights and heights. Several recent studies have shown a strong correlation between maternal and infant birthweights[164 165].

Magnus et al.[81] on analyzing data from a study of twins concluded that 60% of the variance in birthweight could be explained by genetic factors and only 10% was attributable to the adult parental variables.

c. Gender of the baby: Male babies are at twice the risk of developing macrosomia as female babies. Our population of macrosomic babies had 55% males as compared to 45% females.

d. Ethnicity: North American Aboriginals constituted 8.3% of the total study sample. All other characteristics remaining the same, North American Aboriginal ethnicity predisposed these women to three times the risk of macrosomia in comparison to the Caucasian women. Women in the ethnic category of 'others' and 'Orientals' were found to have a negative correlation with macrosomia, though the last two categories did not achieve statistical significance at $p<.05$.

Factors so far listed suggest a parental genetic and constitutional influence on determination of newborn's birthweight.

Some of the other non-modifiable predictors are as follows:
e. Parity: Parity ≥ 2 increases the risk for macrosomia by more than two times compared to a nulliparous woman.

f. Maternal age: Maternal age ≤ 17 years increases the risk by 3 times. Previous studies have suggested conclusions to the contrary, suspecting inadequate nutritional supplementation coupled with pre-term delivery in these gravidas resulting in smaller babies[159 160 161]. Inadequate nutritional supplementation in these adolescent mothers has mainly been attributed to a lack of guidance and resources and an unhealthy life style. Since we included only term (>36 weeks), healthy babies in our study; possibly teens delivering near term are at higher risk of producing macrosomic babies than other age groups. We had only 17 subjects in this category of adolescent mothers. However, further studies examining issues of preterm deliveries and SGA in adolescent mothers with adequate sample size will clarify the issue.

II MODIFIABLE PREDICTORS

The most opportune period to institute preventive measures through the modifiable predictors could be the pre-pregnant or the early pregnant state. Modifiable predictors are of particular interest not only because of their predictive value but also because of their amenability to alteration. The predictors in this category can be modified to some extent in order to limit the baby size.

a. Pre-pregnancy weight: A woman weighing 120 kg before pregnancy is at about 5 times the risk of developing a macrosomic baby than an average weight woman weighing 61 kg (average weight among women weighing <90 kg). Similarly one weighing 105 kg is at 3.4 times the normal risk.

Average birthweight in an 'obese non-GDM' is 3655g±442 which is 207g more than the population average birthweight of 3448g±471. Further implications of obesity on newborn macrosomia are discussed along with glucose intolerance.
b. Smoking is negatively correlated with macrosomia. Every additional five cigarettes smoked per day decrease the risk of macrosomia by 1.5-fold. Average birthweight among smokers vs. non-smokers was 3322g±438 vs. 3502g±475.

c. Weight gain in pregnancy: Optimal weight gains are different for women who begin pregnancy at different nutritional levels. Pre-pregnancy weight and pregnancy weight gain have been shown to be additive in their effect on birthweight[162]. Obese women need to gain the least amount of weight during pregnancy in order to limit the baby size[163].

d. Gestational age: Obstetrical interventions in the form of early and planned pre-term induction of labor or elective cesarean section are not uncommon on suspicion of a LGA baby, more so among impaired glucose tolerance group of women. Univariate analysis had revealed that gestational age of 40-42 weeks had a higher percentage of macrosomic babies than the gestational age of <40 weeks or >42 weeks. The average birthweight in the category of 40-42 weeks gestational age is greater by 250 g than the birthweight in the category of 36-40 weeks gestational age; whereas in babies born after 42 weeks of gestation, the average birthweight (3363g+369) starts falling.

Our finding of fewer macrosomic newborns among >42 weeks post-mature newborns has a biological plausibility. The dwindling placental function in pregnancies after 42 weeks of gestation leads to diminished substrate availability and deceleration of fetal growth.

e. Glucose intolerance: Following the Second International workshop-conference on GDM; SOGC and the Canadian Task force guidelines[108] in Canada have recommended that all pregnant women be screened for GDM, and if diagnosed be treated for the same. Therefore, the effect of glucose abnormality in GDM on the outcome of macrosomia is confounded by treatment or control of the plasma glucose level. However, Langer[129] has recently shown that treatment of GDM, if not highly intensive may only normalize the plasma glucose values without preventing accelerated growth in the fetus. As per his findings, we should have encountered an increased incidence of macrosomia in our GDM population (if it existed), as glucose control in our study population was not as strict as suggested by Langer in his intensive therapy group.

Women in the GDI (screen + and OGTT -) group represent a group possibly as close to a non-intervened albeit untreated group of glucose intolerance as is currently feasible. The available sample size allows us to detect a difference of approximately 125 g in birthweight between GDI group and the rest of the population at p<.05 and power of 90%.

By univariate analysis, iintermediate (GDI) or gestational diabetes mellitus (GDM) were not found to be statistically significantly correlated with the increased risk of macrosomia. On stratifying into obese and non-obese groups (table 4.12 and 4.13), GDI category in the non-obese subgroup had a proportion of macrosomic babies significantly different from the non-obese non-GDM group at p<.05. By multivariate model, the GDI group had an OR of 1.6, 95% CI 0.99-2.7 which is of doubtful statistical significance.

Since there was a trend towards an increased incidence of macrosomia in the GDI group (p>.05), stratification into lean and obese sub-groups showed that the overall proportions of macrosomia are much more in the obese group *irrespective of the levels of glucose intolerance*. Although there is a tendency towards an increased risk of macrosomia in the GDI group of lean women (p>.05), the average birthweight of 'non-obese GDI' is no different than the population average (i.e. 3451g±493 vs. 3448g±471). The average birthweight among 'obese GDI' is 166 g more than the population average (3614g±595 vs. 3448g±471). Similarly, the average birthweight among 'obese GDM' is 69 g more than the total population average; whereas, average birthweight of 'non-obese GDM' is no different from the population average birthweight (3443g±457 vs. 3448g±471). Differences in birthweight of less than about 150 grams would not likely be clinically significant and have a questionable clinical applicability.

In addition, there seems to be no synergistic or potentiating effect of glucose intolerance (GDI or GDM) on obesity for development of macrosomia. In fact, we can not categorically comment on our finding of statistically non-significant interactive effect between maternal obesity and GDM for the outcome of macrosomia, because GDM subjects receive treatment with a goal to normalize plasma glucose values, thereby eliminating the possible morbid effect of high glucose levels on the newborn's birthweight.

Of the 50 GDM women in the study sample, 37 were on diet therapy and 13 were on diet+insulin therapy. 46% of the insulin treated women were obese (≥30BMI), whereas only 16% were obese in the diet therapy group. Looking at the birthweight and maternal characteristics of the 'diet therapy only' group (n=37) vs. the 'insulin+diet therapy' group (n=13), birthweight was 3515g±540 vs. 3706g±437 and average maternal weight and BMI were 64.43kg±15.3 vs. 80.4kg±28.8 and 24.1kg/m^2±5.1 vs. 29.7kg/m^2±8.3 respectively. Seemingly, the increased birthweight in insulin+diet therapy group is possibly explained by the maternal obesity component more than the glucose intolerance per se. Otherwise there should have been no difference in newborn's birthweight in insulin+diet therapy group from the population average, assuming that insulin normalizes the plasma glucose values and prevents macrosomia. Since there were fewer obese subjects in the diet therapy group, it might have been responsible for a small difference in mean birthweight between the diet therapy group and the population average.

Plasma glucose values of GCT and OGTT (f,1hr, 2hr, 3hr) were not significantly different between the macrosomics (by absolute weight criteria as well as by LGA criteria) and the non-macrosomics, both in the GDI and the GDM groups. Macrosomia was not associated with the degree of glucose abnormality in GCT or OGTT levels.

The finding that the average of fasting and the average of post-prandial glucose values among GDM treated subjects were found to be statistically significantly different between the macrosomics and the non-macrosomics (4.7 vs. 5.3 and 5.5 vs. 6) leads us to believe that the birthweight is related to the level of glucose control in the third trimester. However, the clinical significance of the average difference amounting to 0.6 units between the macrosomics and the non-macrosomics, of the tests performed by the pregnant women on home glucometer needs to be ascertained. The consensus statement[136] on Self-Monitoring of Blood Glucose (SMBG) states that approximately 50-70% of individuals who receive some sort of formal training are capable of obtaining a result within 20% of the reference method. The most common reason for errors in SMBG is failure to follow instructions regarding proper application, timing, and removal of the blood sample. Since the total span of training, learning and feedback on accuracy, of the tests performed by gestational diabetics is less than 12 weeks, the test results may not be as reliable as are generally assumed. It is important to mention here that on closer questioning, approximately 20% of the GDM women in our study population admitted to non-compliance or partial-compliance with the treatment plan (therapy or testing on glucometers or both). Besides, the multivariate model did not reveal any significant independent associations between the outcome of macrosomia and the plasma glucose levels of GCT or OGTT or the average of fasting or post-prandial glucose values. What is clinically relevant is not purely the correlations of macrosomia with plasma glucose values but the difference in birthweight and attendant morbidity if any, as a result of these statistically different plasma glucose levels.

Regarding plasma glucose levels of GCT and OGTT, our findings do not agree with conclusions by Langer et al.[5] and others[16 74 100] that there is an increasing incidence of macrosomia with increasing 2-hour values on the OGTT or with abnormal 50g screening values. Tallarigo et al.[74] in a study of borderline glucose intolerant women reported an increased incidence of macrosomia in women with higher 2-hour plasma glucose levels of the oral 3-hour GTT. They did not consider any correction of birth weight for other factors known to affect birth weight, such as gestational age, race, socioeconomic status, smoking status, maternal age, parity, body mass index or maternal weight gain. Recently, Langer et al.[129] concluded that intensified management improves pregnancy outcome. The intensified management group had a rate of macrosomia (LGA 13.1%) similar to that found in the non-diabetic controls. In contrast, the conventional management group showed rate of macrosomia (LGA 20.1%) comparable to that previously reported for women with GDM (20-30%). This study used different criteria for diagnosis of GDM thereby classifying 10% of the screened population as gestational diabetic. In our study, with the so-called 'conventional' treatment (as described by Langer) of GDM, we found no statistically significant difference in the rate of macrosomia between gestational diabetics who received treatment, intermediate group (GDI i.e. no-treatment group) and the rest of the population. In Langer study the mean birthweights in the three categories of control group, conventional therapy group and intensified group were 3239±658g, 3340±635g and 3250±647g, respectively.

What remains to be ascertained includes:

(1) the clinical relevance of less than 150 grams difference in birthweight due to glucose intolerance status and its implication on the increased risk of birth trauma.

(2) the role of non-compliance on macrosomia and other concomitant neonatal morbidities.

(3) correlation between plasma glucose values, particularly third trimester post-treatment plasma glucose values, and accelerated fetal growth with associated morbidities with a larger sample size.

Conclusions

I Pre-pregnancy weight, weight gain in pregnancy and previous history of macrosomia are the most important predictive factors for newborn macrosomia; and the first two of these predictors are modifiable.

II There is no predictive value of plasma glucose values of glucose screen test and oral glucose tolerance test for macrosomia.

III Therapeutic strategies for GDM are driven by consensus or inference, rather than by direct evidence about favorable changes in key endpoints. Despite third trimester plasma glucose level differences between macrosomics and non-macrosomics, there is little in this study to substantiate the wide recommendation of universal screening and tight glycemic control among GDM women.

Increased fetal growth in macrosomic newborns may be more related to the metabolic abnormalities associated with obesity than to those associated with well-controlled gestational diabetes mellitus. Our data suggest that we should concentrate more on containment of excessive pre-pregnancy weight and weight gain during pregnancy rather than on glucose intolerance. Until the controversy regarding the role of glucose intolerance in development of macrosomia and associated neonatal marbidities is settled, we are not justified in subjecting the total population of pregnant women to the economic, social and emotional disadvantages of being so treated. In addition, the health care system is being taxed without concrete evidence of *effectiveness of treatment* other than near normalization of plasma glucose values in gestational diabetics.

The suggested morbidity due to higher levels of glucose in GDM subjects is confounded by the therapeutic measures aiming to normalize the glucose levels. Therefore, it is not possible to study the effects due to higher plasma glucose levels without suspending treatment (in a clinical trial) for glucose abnormality in GDM subjects. In view of a doubtful increased risk of macrosomia among GDI group of women and subtle differences in plasma glucose values in third trimester between macrosomics and non-macrosomics; *a randomized, controlled trial of treatment vs. no-treatment of GDM subjects could only conclusively ascertain an absolute risk and ultimate morbidity due to gestational diabetes mellitus.*

Implications for care

Diet therapy and exercise therapy are the mainstay of therapeutic strategy for obese women. Possible interventions may include: community, family or individual nutrition education and promotion of the balanced diet.

Implications for research

I There is a significant association between gestational diabetes mellitus and maternal obesity. Whether or not impaired glucose intolerance, in itself, is causally related to adverse outcomes of pregnancy remains to be established. The outcome of newborn macrosomia is an intermediate morbidity measure. The clinical relevance of macrosomia is in relation to shoulder dystocia, birth trauma and birth asphyxia; the ultimate morbidities of concern. Proportion of birth trauma or shoulder dystocia or birth asphyxia or any of the suggested metabolic abnormalities in babies of GDM subjects is so low that examining these measures individually will require a mammoth sample size. We have no set criteria for a cummulative scoring system or a tool like 'morbidity index' for adverse neonatal and/or maternal outcomes due to glucose abnormality in pregnancy. Before planning a RCT of treatment versus no-treatment, it is critical to develop a 'morbidity index' that relates increasing glucose intolerance to higher risks of adverse maternal-fetal outcomes while adjusting for confounding factors present in maternal characteristics.

II We should focus on testing interventions to normalize women's weight before pregnancy or during the inter-pregnancy interval and further exploring the best strategy to contain pre-pregnancy weight and weight gain during pregnancy.

III Exploring usefulness, proper time and duration of exercise therapy.

B. Predictors of disproportionate growth

There is very little information on the determinants of disproportionate fat distribution in newborns. It has often been stated that the measurements of muscle plus fat (MAC) and body proportionality (MAC:HC, PI, AC:HC etc..) may be important adjuncts to birth weight, length, and head circumference in the nutritional assessment of newborns in utero. The role of these factors in shoulder dystocia has been stressed by Modanlou et al.[19]. These measurements may also be used as tools to predict neonatal metabolic complications in the early perinatal period[32].

Univariate as well as multivariate techniques have revealed that birth weight is the only predictor of the so-called disproportionate fat distribution. About 12-20% of the variance in these measures is explained by birthweight. None of the other factors such as gender, gestational age at term, maternal pre-pregnancy weight, weight gain, parity, maternal height, maternal age, glucose tolerance status, smoking independent of its effect due to birthweight or ethnicity have any independent association with these measures of growth.

Conclusions

We have found no predictors of increasing ponderal index, MAC:HC and AC:HC i.e. the measures of disproportionate fat distribution, even among those with >90th percentile values of PI, MAC:HC and AC:HC, other than the birth weight itself. We did not include pre-gestational diabetic subjects in our study, therefore we can not comment on the impact of more severe levels of glucose metabolic abnormality on disproportionate fat distribution.

Implications for further research

Possibly, more sensitive techniques should be examined and standardized for ascertaining disproportionate fat distribution in the newborn, so that we can conclusively explain existence/non-existence of this entity of disproportionate fat distribution in macrosomic babies. The clinical significance of these subtle differences in disproportionate fat distribution requiring any more sensitive measures is debatable.

C. Nomograms

Data on normative anthropometric measurements have been presented as tables of 10th, 50th and 90th percentile values of the anthropometric measurements on birthweight. To my knowledge, these tables are the first ever compiled by percentile values on measures of fat distribution in the newborns.

These tables can possibly be utilized by:

a) the pediatricians for purposes of aberrant growth pattern recognition at birth, such as hydrocephaly, microcephaly and achondroplasia etc..

b) the nutritionists for projecting normal nutritional standards in -utero.

c) the obstetricians and perinatologists for reference regarding a difficult delivery and subsequent birth trauma.

CHAPTER 10

LIMITATIONS OF THE STUDY

If I were to design and conduct the same study again; I would like to make the following amendments:

A. Ideally have 100% compliance with screening (at least during the study period) for gestational diabetes mellitus in the pregnant population i.e. without any initial filter of subjects at the obstetrician's office.

B. Change recruitment pattern from a 'convenience sample' to a 'random sample'. No recruitments were made on the weekends and as 'an early discharge program after delivery' was in effect at both the participating hospitals, patients generally left hospital by 48 hrs after delivery. As a result, the patients delivering on weekends were underrepresented in the sample. It would be unlikely that this sampling procedure made a significant difference to the analysis or the results.

C Again, ideally have an absolute uniformity of therapeutic measures between the two participating hospitals. Cut-off plasma glucose levels for initiating insulin administration at the RAH were > 5.5 mmol/l for fasting and >6.5 mmol/l for post-prandial; whereas at the Grey Nuns, the respective levels were >5 mmol/l and >6 mmol/l. Out of 1000 subjects, 143 subjects were recruited from the Grey Nuns hospital.

D. Ideally, have a 'non-intervened' GDM group (untreated) for analysis. With the existing design, the true relative risk due to GDM can not be ascertained; as once GDM is diagnosed, treatment is currently not withheld due to ethical reasons.

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Appendix:I

GESTATIONAL DIABETES MELLITUS AND FETAL MACROSOMIA
MOTHER'S DATA ENTRY FORM

STUDY NO
HOSPITAL NO
Physician In-charge

PATIENT"S NAME:
PATIENT"S AGE :
Husband's Height :
Husband's Weight :

Pre-PregnancyWt

<90Kg	1
90-120Kg	2
>120Kg	3

Maternal Birth Weight gms

Smoker ( )
Yes (1) No (2)
If (1); no. of cigarettes/day___

Height cms
BMI

<28	1
28-31	2
>31	3

Alcohol ( )
Yes (1) No (2)
If (1); no. of Vs/day________

Previous Macrosomic Infant YES/NO

OBSTETRICAL HISTORY:

LMP__________

Weight gain during pregnancy ________ kg

Parity

Gestational Age ________wk

Mode of Delivery:
(a) vaginal : spontaneous / induced / forceps
(b) c/s : elective / emergency

PLASMA GLUCOSE STATUS :

1 Negative **50 gms** Glucose Screening Test (-)

2 Intermediates **50 gms** Glucose Screening Test (+) & **100 gms** Oral Glucose Tolerance Test (-)

3 Positive **50 gms** Glucose Screening Test (+) & **100 gms** Oral Glucose Tolerance Test (+)

Result of the glucose challenge test:

Result of OGTT :

Diet vs Insulin control

Average (weekly) fasting blood glucose:

Average (weekly) 2hr blood glucose:

REMARKS:

Date:

Appendix :II

GESTATIONAL DIABETES MELLITUS AND FETAL MACROSOMIA
NEONATE'S DATA ENTRY FORM

STUDY NO : **BABY NAME :**

Hospital No (Baby) : Sex : M / F
Hospital No (Mother) : Date of Birth :

ANTHROPOMETRY

BirthWeight Grams Body Mass Index :

Height cms Ponderal Index :
(wt.in $gms^3 * 100$/ht in cms)

Head Circumfrence cms

Mid- Arm Circumfrence cms MAC/HC :

CORD BLOOD BIOCHEMISTRY

Glucose level : IGF 1 :

Insulin level : IGF BP 1 :

BABY'S STATUS

Gestational Age wks Congenital Anomaly Yes/No

Birth Trauma Shoulder Dystocia Yes/No

REMARKS:

Macrosomia/Non Macrosomia

Proportional/Disproportional

Date:

Royal Alexandra
HOSPITAL

Appendix: III

GESTATIONAL DIABETES MELLITUS AND FETAL MACROSOMIA

INFORMATION SHEET AND CONSENT FORM FOR THE PATIENT

Investigators: Dr Okun & Dr Verma

I have received information regarding the above titled study and I understand that the main purpose of the study is to ascertain factors influencing birthweight and size of the newborn baby. Physical features and measurements of newborns with birthweight more than 4000 gms will be compared with those of birthweight less than 4000 gms.

I understand that no research related painful procedure will be involved and most of the information will be gathered from hospital records of my routine investigations and a short interview with me during my stay in the hospital at the time of baby's birth. Baby will be weighed and will have measurements of his/her head, arm and abdomen taken with a measuring tape.

I further understand that within this study, all information about me or my baby will remain confidential and will serve only for the purposes of research analysis. Should I decide to withdraw my participation from the study at any time, I may do so without any prejudice to me or my baby's overall health care.

Any pertinent questions that I asked, have been answered to my satisfaction and I understand that I may call Dr Okun or Dr Verma at 477-4812 in case of any further enquiries.

I have received a copy of the informed consent and agree to participate voluntarily in this study.

(Patient's Name)	(Patient's Signature)
(Baby's Name)	(Witness's Signature)
Date:	(Investigator's Signature)

DISTRIBUTION: *WHITE* - OFFICE COPY *CANARY* - PATIENT'S COPY

PERI. 003 Jan. 93

BAKER CLINIC

10025 - 106 STREET
EDMONTON, ALBERTA
T5J 1G4

DEPARTMENT OF
INTERNAL MEDICINE

TEL. (403) 423-6911
FAX (403) 426-2223

OUR CHART

16 July 1992

Dr. Nan Okun
c/o Perinatology Clinic
Royal Alexandra Hospital,
10240 Kingsway Avenue,
Edmonton, Alberta,
T5H 3V9

Dear Dr. Okun:

This letter will confirm my participation in the proposed study on the relative importance of gestational diabetes mellitus in the development of fetal macrosomia. As per the study protocol, my involvement in this study would involve confirmation of the diagnosis of gestational diabetes in patients attending the Royal Alexandra Hospital Diabetic Program as well as their on going management during the pregnancy and the recording of their relevant glucose data. These patients will be attending out Outpatient Diabetes Clinic where they will receive full instruction in their diabetic condition, home blood glucose monitoring techniques and diabetic diet. Those deemed necessary for additional glucose management with insulin will be treated in the usual fashion as per our criteria.

We look forward to participating in this study with you.

Sincerely yours,

C. KEITH BOWERING, M.D., F.R.C.P.C.
Medical Director, Diabetes Care Programs
Royal Alexandra Hospital

CKB/jw

University of Alberta
Edmonton
Canada T6G 2S2

Division of Endocrinology and Metabolism

362E Clinical Wing, Heritage Medical Research Centre
Telephone (403) 492-6011
Facsimile (403) 492-8291

Edmond A Ryan, MD, MRCPI, FRCPC

July 24, 1992

Dr. Nan Okun
Obstetrics & Gynecology
Royal Alexandra Hospital
10240 Kingsway Avenue
Edmonton, AB
T5H 3V9

RE: **"MACROSOMIA: THE RELATIVE RELATIONSHIP OF BIRTH WEIGHT TO PREPREGNANCY AND PREGNANCY VARIABLES"**

Dear Nan:

I would be pleased to help you in the performance of this study. Gestational diabetes is an important area and resolution of its importance versus maternal obesity in causing macrosomia is a question that requires careful study. I thus welcome the opportunity to collaborate with you and would be pleased to offer any assistance I can.

Yours sincerely,

Eddie

Edmond A. Ryan, M.D.
Division of Endocrinology

EAR/vgf

APPENDIX IV

Dr. Robert E. Lefebvre, M.D., FRCPC
PROFESSIONAL CORPORATION
Nephrology

Dr. Mitchell S. Akman, M.D., FRCPC
PROFESSIONAL CORPORATION
Endocrinology & Metabolism

INTERNAL MEDICINE
805 PROFESSIONAL BUILDING
10830 JASPER AVENUE
EDMONTON, ALBERTA
T5J 2B3
PHONE: 426-4106

July 20, 1992

Dr. Nan Okun
Royal Alexandra Women's Centre
10240-Kingsway Ave.
EDMONTON, Alta.
T5H 3V9

Dear Dr. Okun:

After having read the proposal that you presented on contributing factors to macrosomia in gestational diabetes I can say that I whole heartily support this project. I would be more than happy to coordinate things at the Edmonton General (Grey Nuns Hospital). As you know I am involved in both diagnosing and managing the gestational diabetics from the Grey Nuns Hospital and would have no trouble providing you the necessary information for this project.

Determining the factors which cause macrosomia in this patient population would be of great benefit. I hope this is of assistance.

Yours sincerely,

M. S.

Mitchell Akman, M.D.

MSA/lr

Grey Nuns Hospital

1100 Youville Drive West Edmonton, Alberta T6L 5X8 Tel. (403) 450-7000 Fax. (403) 450-7500

July 20, 1992

To whom it may concern:

This letter is an acknowledgment that I am aware and approve of the study "The Relative Importance of Gestational Diabetes Mellitus in the Development of Fetal Macrosomia". I will discuss this protocol with members of the attending staff and whom I am sure will agree to entering patients into the study, pending individual consent. The protocol will be assessed by our Research Steering Committee when I have obtained the final protocol and funding information.

Yours sincerely,

N. Schuurmans, MD, FRCS(C)
Clinical Head, Department of Obstetrics & Gynecology

faxed July 20, 1992 - original to follow by mail.
hc

Member Caritas Health Group

Division of Maternal-Fetal Medicine
University of Alberta

UNIVERSITY OF ALBERTA HOSPITALS
NEONATAL SERVICES 492 - 6187
PERINATAL SERVICES 492 - 6572

ROYAL ALEXANDRA HOSPITAL
WOMEN'S CENTRE
NEONATAL SERVICES 477 - 4644
PERINATAL SERVICES 477 - 4815

17 July, 1992

TO WHOM IT MAY CONCERN

re: The Relative Importance of Gestational Diabetes in the Development of Fetal Macrosomia

The research proposal prepared by Drs. N. Okun, A. Verma, G. Flowerdew, and D. Morrish has been reviewed in detail by myself and the Department of Obstetrics and Gynecology. The research proposal is found to be well-done and asks a relevant question.

The Department of Obstetrics and Gynecology has shown unanimous support for this research proposal and are willing to have their patients enrolled in this study and to perform the tests that are required to fulfill the inclusion criteria.

Yours truly,

Nestor N. Demianczuk, M.D., FRCSC
Chief, Dept. of O & G
Royal Alexandra Hospital

NND/jc

ROYAL ALEXANDRA HOSPITAL 10240 Kingsway, Edmonton, Alberta T5H 3V9
UNIVERSITY OF ALBERTA HOSPITALS 84 Avenue & 112 Street, Edmonton, Alberta T6G 2B7

University of Alberta
Edmonton
Canada T6G 2R7

Department of Obstetrics and Gynaecology
1D1 Walter C Mackenzie Health Sciences Centre
Telephone: (403) 492-6636 Fax: (403) 492 7720
BF (Peter) Mitchell, Professor and Chairman

July 15, 1992

Dr. Nan Okun
Division of Maternal-Fetal Medicine
Royal Alexandra Hospital
1929 Women's Centre
10240 Kingsway Avenue
Edmonton, Alberta
T5H 3V9

Dear Nan:

I just read your proposal regarding a prospective epidemiologic study of the association of gestational diabetes mellitus with macrosomia and fetal proportional growth. I think it is an excellent study. I am quite enthusiastic that Anila Varma is an excellent graduate student to have on this project. Her commitment is indicated by her registration in the courses in Epidemiology and Biostatistics and her abilities by the good grades she has obtained. The research question is a very relevant one and one which I think you will be able to answer with your proposal. The results could have a significant influence on our approach to diabetes mellitus diagnosed during pregnancy.

We have discussed your proposed protocol with our staff members here at University of Alberta Hospitals. There is general agreement and enthusiasm. I am confident our attending staff will cooperate fully with proper screening and assistance in patient recruitment.

Many thanks for including our hospital in your study. I am looking forward to seeing the results. Please let me know if there is anything further I can do to help with the project.

Best personal regards.

Peter

B.F. Mitchell, M.D.
Professor and Chairman

BFM/dac